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Elevated Responding to Safe Conditions as a Specific Risk Factor for Anxiety Versus Depressive Disorders: Evidence From a Longitudinal Investigation

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Abstract

The current study evaluated the degree to which startle reflexes (SRs) in safe conditions versus danger conditions were predictive of the onset of anxiety disorders. Specificity of these effects to anxiety disorders was evaluated in comparison to unipolar depressive disorders and with consideration of level of neuroticism. A startle paradigm was administered at baseline to 132 nondisordered adolescents as part of a longitudinal study examining risk factors for emotional disorders. Participants underwent a repetition of eight safe-danger sequences and were told that delivery of an aversive stimulus leading to a muscle contraction of the arm would occur only in the late part of danger conditions. One aversive stimulus occurred midway in the safe-danger sequences. Participants were assessed for the onset of anxiety and unipolar depressive disorders annually over the next 3 to 4 years. Larger SR magnitude during safe conditions following delivery of the aversive stimulus predicted the subsequent first onset of anxiety disorders. Moreover, prediction of the onset of anxiety disorders remained significant above and beyond the effects of comorbid unipolar depression, neuroticism, and subjective ratings of intensity of the aversive stimulus. In sum, elevated responding to safe conditions following an aversive stimulus appears to be a specific, prospective risk factor for the first onset of anxiety disorders.

Keywords

startle response; emotional disorders; anxiety disorders; depressive disorders; risk factors

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Increasingly, attention is being given to the role of elevated defensive responding to conditions that cue safety in the context of threat as a potential mechanism underlying the onset and maintenance of anxiety disorders. In other words, the tendency to become anxious in response to cues that do not signal danger, but that occur within the same context as other cues that do signal danger, may represent one pathway through which the experience of negative events leads to pervasive anxiety in some individuals. At least two major lines of research point to such a mechanism, one involving fear conditioning and the other involving fear potentiated startle. The current report extends the latter line of research.

Specifically, in the fear conditioning literature, individuals with anxiety disorders have been shown to less inhibition of fear responding to a conditional stimulus minus (CS−) (not previously paired with the unconditional stimulus (US)) relative to controls (see Craske et al., 2008; Lau et al., 2008; Lissek et al., 2005 for a review; Lissek et al., 2009; Waters, Henry, & Neumann, 2009). This has been interpreted within an associative framework as impaired learning of inhibition of fear responses to safety cues (CS−; Davis, Falls, & Gewirtz, 2000), which may be partly driven by greater stimulus generalization between conditional stimulus plus (CS+) and CS− cues (Lissek et al., 2010).

In terms of fear-potentiated startle, studies have repeatedly shown anxiety-related elevations in psychophysiological responses of startle eyeblink reflexes during conditions that signal safety, but not in response to conditions that explicitly signal threat (e.g., of electric shock, air blasts to the larynx, complete darkness, or exposure to threatening faces; e.g., Craske, Waters, et al., 2009; Grillon & Ameli, 1998; Grillon, Ameli, Goddard, Woods, & Davis, 1994; Grillon & Morgan, 1999; Grillon, Morgan, Davis, & Southwick, 1998; Pole, Neylan, Best, Orr, & Marmar, 2003; Waters, Neumann, Henry, Craske, & Ornitz, 2008). These effects have been observed in individuals (across the age range) who have anxiety disorders, as well as in children and adolescents who are at risk for anxiety disorders (e.g., Grillon, Dierker, & Merikangas, 1998; Grillon et al., 2005). For example, adolescents who were highly behaviorally inhibited and developed anxiety disorders showed elevated startle reflexes to safe cues, but not to danger cues (Reeb–Sutherland et al., 2009). Also, we found that higher levels of neuroticism (a risk factor for anxiety disorders; Krueger, Caspi, Moffitt, Silva, & McGee, 1996), were associated with elevated startle reflex magnitude to safe conditions within a repetition of safe-danger sequences in adolescents (Craske, Waters, et al., 2009). The data in at-risk samples implicate elevated responding to safe conditions as a feature of fear responding that contributes to the onset of anxiety disorders.

We sought to expand upon this line of research by evaluating the role of responding to danger and safety conditions, assessed within a fear-potentiated startle paradigm, as a risk factor for the subsequent development of anxiety disorders. Furthermore, we sought to address the degree to which responding to safe conditions was specifically predictive of anxiety disorders, relative to emotional disorders in general. This is an important question given the high rate of comorbidity between anxiety and depression (Brown, Campbell, Lehman, Grisham, & Mancill, 2001; Kessler, Chiu, Demier, & Walters, 2005), and the continuing search for factors that are common to anxiety and depression (e.g., Krueger, 1999; Mineka, Watson, & Clark, 1998; Watson, 2005) as well as factors that are unique to each (see Craske, Rauch, et al., 2009). Only one study has examined differential effects of anxiety and depression upon startle reactivity in a fear-potentiation paradigm (Melzig, Weike, Zimmermann, & Hamm, 2007). Panic disorder patients without depression showed startle potentiation to threat of shock, relative to controls, whereas panic disorder patients with depression showed startle attenuation, suggesting an attenuation of anxiety-related responding by depression. Other data show that higher scores on depression inventories, along with other indices of negative affectivity or dysphoria, are associated with lower startle reflex magnitude to personally relevant fearful imagery in individuals with mixed

anxiety disorders (Lang & McTeague, 2009). These data suggest differences in fear responding at the behavioral level between anxiety and depression. Clearly, there is need for more research investigating risk factors which are unique to anxiety disorders versus depression or are a common risk for both conditions.

Thus, the aim of the present study was to examine the extent to which elevated startle responding during safe conditions versus danger conditions in a fear-potentiation paradigm was uniquely predictive of the onset of anxiety versus unipolar depressive disorders over the ensuing 3 to 4 years. In light of prior findings, we hypothesized that elevated startle reflexes during safe conditions would predict the onset of later emotional disorders, whereas startle reflexes during danger conditions would not. Also, given that neuroticism is a risk factor for both anxiety and depression and given our cross-sectional findings for neuroticism (i.e., Craske, Waters, et al., 2009), elevated startle reflexes during safe conditions might predict the onset of both anxiety and depression. On the other hand, given the evidence that depression attenuates fear-potentiated startle and fear-imagery startle in anxious adults (Melzig et al., 2007; Lang & McTeague, 2009), an alternate hypothesis is that elevated startle reflexes during safe conditions are specific predictors of the onset of anxiety versus depression and over and above variance accounted for by neuroticism.

Method

Participants

Participants (N = 132) were part of a larger two-site, prospective study (the Youth Emotion Project, YEP). Three cohorts of high school juniors (mean [M]$_{age}$ = 16.1, [standard deviation] SD = 0.47) were recruited over consecutive years from high schools in suburban Chicago and suburban Los Angeles. The participants in the larger study (N = 627) were selected based on the Neuroticism (N) subscale of the Eysenck Personality Questionnaire—Revised (EPQ-R-N; Eysenck & Eysenck, 1975). Participants with high EPQ-R-N scores (i.e., “at risk” for developing emotional disorders; Clark, Watson, & Mineka, 1994; Hayward, Killen, Kraemer, & Taylor, 2000; Krueger et al., 1996), were oversampled to overcome statistical problems associated with low base rates of incidence of emotional disorders: 58.7% scored in the top third, 23.1% in the middle third, and 18.2% in the bottom third (see Zinbarg, 2010, for more detail).

Approximately half of males and females in each third of the EPQ-R-N distribution were randomly invited to participate in the startle protocol; of those invited, 209 completed the protocol, of whom 24 did not have usable data (see below). Those who did not participate either declined to participate, could not be scheduled, or did not complete the experiment because of difficulty getting to the startle laboratories. Of the 185 with usable data, 53 met diagnostic criteria for a psychiatric diagnosis at baseline and were excluded from the current analyses.[1],[2] The final sample of 132 participantss were 64.4% female, ranged from 16 to 18 years (M = 17.01 years, SD = .45), and were racially and ethnically diverse, with 45.5% Caucasian, 21.2% Hispanic, 9.1% African American, 6.1% Asian American, 0.8% Native American/Pacific Islander/Alaskan Native, 12.1% multiracial, and 5.3% in another racial or ethnic group. The age, gender, and neuroticism of this subsample of 132 did not differ significantly from the remainder of the sample (n = 405), ps > .06, although there were more

[1]To be conservative, we checked whether participants met threshold for most, but not all, diagnostic symptom criteria for a disorder (referred to as not otherwise specified, NOS). However, none of the remaining 132 participants were diagnosed as NOS.

[2]Five participants retrospectively reported a history of an anxiety disorder (n = 2) or a depressive disorder (n = 3), two of whom reported no age of onset and three reported an onset more than 1 year prior. These cases were included given good evidence for unreliability of retrospectively reported diagnostic history (Andrews et al., 1999), and because their exclusion did not change the pattern of results (see below).

Hispanics in the startle subsample (26.4%) than the remainder of the sample, (17.7%), χ^2 (1) = 4.93, $p < .05$.

Startle Modulation Protocol

Overall design—The fear-potentiation protocol involved eight repetitions of safe-danger sequences, during which an aversive biceps contraction was threatened to occur during the final 15 s of danger conditions only. Auditory startle stimuli were presented throughout, as described below. The protocol also included startle trials before the fear-potentiation protocol, but since responses to these were not modulated by neuroticism in our prior report (Craske, Waters, et al., 2009), they are used only as a baseline covariate herein.

Methods—The experiment commenced with a 5-min resting period, during which particpants watched a muted digital video disk and no startle stimuli were presented. Participants were then fitted with headphones and administered a single startle stimulus to reduce reactivity (not reported). After 16 startle trials (the last eight of which were used as the baseline covariate), repetitions of the safe–danger sequences were presented. Before initiating the safe–danger sequences, participants were given the following instructions:

> In this next part, you will continue to periodically hear the sounds through the headphones and during some periods you may also receive a muscle contraction. When you see on the computer the words “Safe: no contraction will be given,” you can be 100% sure that no muscle contractions will be delivered while those words are on the screen. You will see on the computer screen that a progressing bar will count up the time from 0 to 55 seconds during the period. You may still hear the sounds through the headphones, but you definitely won’t get any muscle contractions. When you see on the computer monitor the words “Danger: contraction may be given,” you may or may not receive a muscle contraction. You will see on the computer screen that a progressing bar will count up the time from 0 to 55 seconds, and if you are going to receive a muscle contraction, it will occur anywhere between 40 and 55 seconds. When the white cross appears in the center of the screen, this is a rest period, and no tones or muscle contraction of any kind will be delivered. During the whole time, you may get a muscle contraction up to three times. After you get it once, it will be a little stronger the next two times.

All particpants actually received only one contraction in the final 15 s of the fourth danger condition, modeled on a procedure used previously (Grillon, Ameli, Foot, & Davis, 1993). The colors of the progressing bars were green in the safe conditions and red in the danger conditions, with a darkening redness in the final 15 s of the danger condition. Two startle probes were presented in each safe and each danger condition, at 5 and 35 or 15 and 45 s, resulting in 32 startle probes total.

Electrophysiological materials, equipment, and data acquisition—Auditory startle stimuli (105-dB, zero rise time, 50-ms white noise bursts) were presented binaurally through stereophonic headphones (Sony, Model MDRV700). Instructions were presented on a color monitor throughout. The biceps contraction was delivered by an electrical muscle stimulation device. The amplitude and latency of startle responses (SRs) were measured by electromyogram (EMG) activity of the orbicularis oculi.

EMG was recorded from electrodes placed beneath the right eye, approximately 10 mm apart edge to edge, and 9 to 11 mm below the lower lid margin. The lateral electrode was placed 5 mm medial to the outer canthus. A vertical electro-oculogram was recorded from electrodes above and below the left eye to facilitate recognition of spontaneous blinks and eye movements. The impedance level of electrodes was 15 KOhm or less. EMG was

amplified by 10,000 with low and high frequency cut-off values of 30 Hz and 1000 Hz, digitized at 1000 Hz, full-wave rectified after analogue to digital conversion, and smoothed with a 2-ms moving average filter.

EMG magnitudes were expressed as the difference between the mean amplitude of the 200 ms of EMG preceding the startle stimulus (SS) and the peak response, between response onset and 104 ms following the SS. Response onset was defined as the first EMG increment between 20 and 80 ms (response onset window) following SS onset exceeding 2 *SD* above the mean baseline and not dropping below that level for more than 10 ms. Eight percent of trials were rejected because of artifact associated with movement or drowsiness (manifested as reduced velocity of spontaneous blinks and slow rolling movements in the electro-oculogram recording), or spontaneous blinks just before the startle stimulus, or excessive EMG during the 200 ms preceding the startle stimulus, and were coded as missing values. Startle responses were scored as zero magnitude on 6.6% of trials due to no observable EMG activity during the response onset window and no reason to reject the trial, and were retained in all analyses. Participants with more than 20 rejected trials ($n = 6$) or more than 17 zero trials ($n = 6$) were excluded. Data were rejected from another five participants who did not receive the muscle contraction and another seven participants with incomplete data. Given the highly skewed nature of startle EMG (Yamada, Yamasaki, Nakayama, & Miyata, 1980), analyses were performed on natural log (ln)-transformed eyeblink data.

The muscle contraction, delivered by a Digital 807 Electrical Muscle Stimulation Device (Everyway Medical Instruments), was a 20.4 mA peak current (i.e., equating to 50 V peak) for .5 sec. The experience of the contraction is one of a very rapid onset, uncomfortable muscle contraction across the biceps for .75sec. The sensation of an involuntary muscle contraction is different from a typical electrical shock which leads to brief localized sensations similar to a quick pinch or pin prick. The intensity level was preset on the basis of pilot testing to represent an uncomfortable but not painful intensity, but was similar to mean voltage levels of shock intensity in studies using shock work-up procedures (Neumann & Waters, 2006); individualized work-up procedures were not chosen, because preexposure to the muscle contraction might have decreased anticipatory anxiety during the safe–danger sequences and/or weakened its aversiveness due to habituation (Baker, Mercier, Gabel, & Baker, 1981). Although participants did not experience the aversive stimulation prior to the procedure, our prior studies using a similar approach (instructions that the stimulation may occur up to three times with increasing intensity) have shown consistently increased affective responding both before and following receipt of the aversive stimulation (Naliboff et al., 2008; Twiss et al., 2009).

Subjective rating of intensity and unpleasantness of stimuli—Participants rated separately the intensity and unpleasantness of the muscle stimulation and the startle tone using Gracely Box Scales, which are 0–20 combined numerical analog descriptor scales developed from previously quantified verbal descriptors (Gracely et al., 1978; Heft et al., 1980). Intensity was rated 0 = none, 11 = moderate, 18 = extremely intense. Unpleasantness was rated 0 = neutral, 10 = very unpleasant; 15 = intolerable; 17 = very intolerable.

Diagnostic and Neuroticism Measures

Structured Clinical Interview for the *DSM–IV* (SCID; First, Gibbon, Spitzer, & Williams, 2002)—At baseline, a lifetime SCID version was used; thereafter, annual SCID interviews assessed symptoms occurring since the last interview, generally within the last year (see Zinbarg et al., 2010, for details). When participants met threshold for most, but not all, diagnostic symptom criteria for a disorder, with their symptoms being accompanied by clinically significant distress and/or impairment, a “not otherwise specified” (NOS)

diagnosis was given (n = 9; see Table 2 for details about NOS diagnoses). After completing interviews, interviewers rated the severity of each current diagnosis (including NOS) in the past month using the Di Nardo and Barlow (19898) 0 to 8 clinician-severity rating (CSR) scale, in which scores of 4 or above indicate clinically significant impairment or distress have been present for the past month. For diagnoses that were not current, but which were assigned as having occurred in the interval since the last interview, clinical severity was tied to the interval of time when the individual indicated greatest severity, and was rated as a "case" (corresponding to a CSR ≥4), a possible case (corresponding to a CSR = 3), or "no case" (corresponding to a CSR ≤2).

Diagnostic reliability was assessed in the larger YEP sample by having trained interviewers observe live SCIDs (n = 69). Kappas were good when aggregated across all disorders (.82) and at least acceptable for those individual disorders assessed in three or more cases, including major depressive disorder (.83), social anxiety disorder (.65), generalized anxiety disorder (.85), and obsessive–compulsive disorder (.85). The interrater Pearson r for CSR ratings ranged from .74 for major depressive disorder and specific phobia to .97 for obsessive–compulsive disorder and posttraumatic stress disorder.

Dependent variables included presence or absence of: (1) all anxiety disorders within the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV; (APA, 1994)), including NOS diagnoses, with a CSR ≥4 in the last month, or considered a "case" since the last interview and (2) all *DSM–IV* unipolar depressive disorders, including NOS diagnoses, with a CSR ≥4 in the last month, or considered a "case" since the last interview. NOS diagnoses were included to enhance sample size for first onsets, with the proviso that the symptom presentation was judged to be clinically severe (i.e., CSR ≥4 or a "case").

Composite neuroticism.—To increase the reliability and validity of the measured construct, we used a composite of standardized values from four self-report questionnaires: the Neuroticism scale of the Eysenck Personality Questionnaire (EPQ-R-N; a suicide item was omitted due to Institutional Review Board concerns, and item 12 was excluded because factor analysis showed it did not load well with the other items; Eysenck & Eysenck, 1975), the Big-Five Mini-Markers Neuroticism scale (Saucier, 1994), the International Personality Item Pool-NEO-PI-R (IPIP-N; http://ipip.ori.org/newNEOKey.htm, extracted 05/16/06), and the Behavioral Inhibition System scale (BIS; Carver & White, 1994), with the latter representing a facet of N, namely trait anxiety, that is also included in the total scores for the EPQ (Mor et al., 2008) and IPIP (see Zinbarg et al., 2010, for details on the psychometric properties of the Neuroticism composite). The EPQ-R-N was administered as part of initial screening, and remaining questionnaires were administered a median of 4 months (range 1–14 months) later.

Procedure

After signing informed consent, participants completed a baseline diagnostic assessment, followed by the startle protocol 1 to 12 months later. The startle experiment was completed with usable data by 75 participants at the University of California at Los Angeles (UCLA) and 57 participants at Northwestern University (NU) who did not meet diagnostic criteria for a current psychiatric diagnosis at baseline. The two laboratories at UCLA and NU used identical hardware, software, manualized procedures, and technician training procedures (the majority [67%] of experiments at each laboratory were run between 3:00 p.m. and 8:00 p.m., with the rest before 3:00 p.m. Participants were seated upright in a sound attenuated room adjacent to the experimental room, inter-connected via intercom and closed-circuit cameras from two angles (UCLA) or one-way mirrors (NU). Participants were instructed to sit quietly and as still as possible throughout the paradigm.

From the time of the baseline interview, participants were assessed diagnostically over the subsequent 4 years with annual SCID interviews. These corresponded to 3 to 4 years after the startle protocol, with the first annual assessment always occurring following the startle protocol.

Statistical Analysis

Startle variable reduction—Four main startle indices were calculated: mean EMG SR during the safe conditions prior to the muscle contraction, the safe conditions following the muscle contraction, the danger conditions prior to the muscle contraction, and the danger conditions following the muscle contraction. Also, within danger conditions, additional analyses were conducted for the preimminent phase (seconds 0–44), when participants knew the stimulation would not be delivered, and the imminent phase (seconds 45–60), when participants knew the stimulation could be delivered. The preimminent phase averaged across startle probes delivered at 5, 15, and 35 s; the imminent phase was comprised of startle probes delivered at 45 s only. Finally, mean EMG SR for the eight trials immediately preceding the safe–danger sequences was calculated and used as a baseline covariate for all analyses.

Regression analysis—A proportional hazards survival analysis (Singer & Willett, 2003) was used to test SRs as predictors of disorder onset. Survival analysis accounts for variability in the number of assessments per participant due to missing data. The mean SR for the eight trials preceding the safe–danger sequences (i.e., baseline SR) was entered into the first block as a covariate for all analyses to account for individual differences in baseline SR. For safe–danger sequences, SR before the muscle contraction was entered in the second block, and SR after the muscle contraction were entered in the third block. For additional analyses of preimminent and imminent phases within danger conditions, preimminent SR before the muscle contraction was entered in the second block, imminent SR before the muscle contraction in the third block, and preimminent and imminent SR after the muscle contraction in the fourth and fifth blocks, respectively.

Participants' time points were censored after disorder onset (e.g., a participant with a diagnosis of an anxiety disorder at Year 1 was deleted from the model for Years 2, 3, and 4). Hazards ratios (HR)[3] are reported with 95% confidence intervals.

Results

Reported Intensity and Unpleasantness of Muscle Stimulation

Overall, participants rated the muscle stimulation as moderately intense ($M = 12.89$, $SD = 3.81$) and annoying to very unpleasant ($M = 8.79$, $SD = 3.89$), on 0–20 point scales.

Safe Versus Danger Effects

A 2 (premuscle contraction, postmuscle contraction) × 2 (safe condition, danger condition) analysis of covariance (ANCOVA) covarying baseline SR was conducted. See Table 1 for descriptive information on SR means and *SD*s. A significant main effect of safe versus danger conditions was observed, $F(1, 410) = 33.83$, $p < .001$, partial $\eta^2 = .08$, with larger SR in danger conditions. A significant main effect of pre- versus postmuscle contraction was observed, $F(1, 410) = 24.45$, $p < .001$, partial $\eta^2 = .06$, with smaller SR following the contraction, as a result of overall habituation. The Pre- versus postmuscle contraction × Safe versus danger interaction was not statistically significant ($p > .18$).

[3]HRs represent the additional risk per unit time associated with any one-unit increase in a given predictor (Singer & Willett, 2003, p. 474): e.g., HR = 20 – 1-unit increase in the covariate is associated with a 20% greater risk for the dependent variable per time point.

Within danger conditions, separate analyses of the Preimminent and imminent phase × Pre- and postcontraction SR were conducted. Significant main effects were observed for preimminent versus imminent phases of the danger conditions, $F(1, 512) = 194.67$, $p < .001$, partial $\eta^2 = .28$, with higher SR during the imminent phases. A significant interaction was observed, $F(1, 512) = 7.04$, $p < .01$, partial $\eta^2 = .01$. Exploration of the interaction revealed that SR during the preimminent phases pre-contraction was significantly higher than preimminent phases post-contraction, $F(1, 257) = 16.76$, $p < .001$, partial $\eta^2 = .06$.

Finally, the effect of site (UCLA vs. NWU) was evaluated and in no case were there differences, *ps* = .07 to .91.

Disorder Onset

Table 2a and b, report the frequencies of anxiety and unipolar depression diagnoses at each time point after censoring. These rates are somewhat higher than epidemiological data, which is to be expected given our oversampling for high levels of neuroticism. That is, of our 132 participants, 12.1% had an onset of an anxiety disorder and 25.8% had an onset of a depressive disorder over the 4 years following the startle paradigm (from approximately 17 to 21 years of age).[4] Table 3 reports the means and *SD*s of the predictor variables. Tables 4 and 5 report the hazard ratios from multivariate survival models described below.

Safe-Danger Sequences Predicting Disorder[5]

Anxiety disorder onset—SR during the safe conditions before the muscle contraction was not significantly associated with anxiety disorder onset ($p = .56$) in the proportional hazards survival analysis.

Higher SR during safe conditions after the muscle contraction was associated with increased risk of anxiety disorder onset (HR = 2.53, $p < .05$, 95% CIs: 1.11–5.83), above and beyond the effects of the SR during safe conditions before the muscle contraction. In a supplemental analysis, we evaluated the degree to which those who developed anxiety disorders had differed from those who did not in terms of SRs during the postcontraction safe condition. A univariate ANCOVA with postcontraction safe condition SR as the dependent variable, baseline and precontraction safe condition SR as covariates, and anxiety disorder status as the independent variable, yielded a significant effect of anxiety disorder status, $F(1, 125) = 4.83$, $p < .05$, with higher SRs in those who developed anxiety disorders.

In the event that anxiety disorders diagnosed at the Year 1 assessment had an onset prior to the startle protocol, we repeated the above analyses excluding Year 1 and excluding the four participants whose first onsets of an anxiety disorder were diagnosed at the Year 1 assessment. Again, higher SR during safe conditions after the muscle contraction was associated with increased risk of anxiety disorder onset over Years 2 through 4 (HR = 5.06, $p < .05$, 95% CIs = 1.17–21.95).

To assess whether the prediction of onset was specific to anxiety versus unipolar depression, the presence of unipolar depressive disorder was entered as a covariate in the proportional hazards survival model: larger SR during safe conditions after the muscle contraction remained a significant predictor of anxiety disorder onset in Years 1, 2, 3, or 4 [HR = 2.76, *p*

[4]Estimates from U.S. epidemiological data indicate that 7.9% of the population had an onset of anxiety disorders between 11 and 21 years of age and 3.5% had an onset of major depression between 14 and 19 years of age (Kessler et al., 2005).

[5]Hazard ratios did not differ when the five participants who retrospectively reported a history of anxiety or depression at baseline assessment were excluded. Similarly, they did not differ when analyses were limited to *DSM* manifestations of anxiety and depressive disorder onsets (i.e., excluding NOS manifestations). Nor did they differ when analyses were limited to participants with diagnoses in the past month at each interview period, for both *DSM* only and *DSM* or NOS manifestations combined.

< .05 (95% CIs: 1.12– 6.82)], as did the presence of depression [HR = 3.26, p < .05 (95% CIs: 1.19 – 8.92)]. Also, when the composite neuroticism measure was entered as a covariate, larger SR during safe conditions following the muscle contraction continued to predict anxiety disorder onset [HR = 2.65, p < .05 (95% CIs: 1.07– 6.24)], as did neuroticism [HR = 2.33, p < .001 (95% CIs: 1.45–3.74)]. Finally, given use of a standardized muscle contraction intensity across all participants, individual differences in self-reported intensity and unpleasantness of the muscle contraction may have influenced the results, and therefore were entered as covariates: larger SR during safe conditions following the muscle contraction continued to predict anxiety disorder onset, HR = 2.91, 95% CIs: 1.19 –7.11. Self-reported intensity and unpleasantness were not significant predictors of anxiety disorder onset (ps > .43).

SR during the danger condition, either before or after the contraction did not predict onset of anxiety disorders (all ps > .74). Also, we analyzed the degree to which SRs during the preimminent and imminent phases, before and after the contraction, predicted anxiety disorder onset. None were significant predictors of anxiety disorder onset (all ps > .19). To assess whether the prediction of anxiety disorders was specific to safe relative to danger conditions after the muscle contraction, pre- and postmuscle contraction SR during danger conditions were entered as covariates. After accounting for these variables, SR during safe conditions postmuscle contraction continued to predict anxiety disorder onset, HR = 2.66, p < .05, 95% CIs: 1.12– 6.32.

Unipolar depression onset—None of the startle parameters during safe conditions or danger conditions, before or after the contraction, significantly predicted unipolar depressive disorder onset (all ps > .19). Nor did the separate analyses of preimminent and imminent phases within the danger condition predict depression onset (all ps > .09).

Discussion

The goal of this study was to evaluate the degree to which SRs in safe conditions versus danger conditions were predictive of the onset of anxiety disorders or unipolar depressive disorders over the subsequent 3 to 4 years. Elevated SRs during safe conditions, after delivery of an aversive stimulus, were predictive of the onset of anxiety disorders; no SR index was a statistically significant predictor of the onset of unipolar depressive disorders. Moreover, elevated SRs during safe conditions continued to significantly predict the onset of anxiety disorders, after entering unipolar depressive disorder status, composite neuroticism, self-rated intensity and unpleasantness of the muscle contraction, and SRs during danger conditions, as covariates. These findings suggest that elevated responding in a safe condition of a threat paradigm is a marker of risk that is specific to first onset anxiety disorders.

Our data demonstrated that the muscle contraction was rated as moderately intense and annoying to very unpleasant, and that SRs were larger during danger than during safe conditions both before and after receipt of the muscle contraction. They were also larger during the imminent than the preimminent phases within the danger conditions, which together indicate that our fear potentiation protocol was successful. Moreover, with this fear potentiation protocol, the hazard ratios indicated that for every 1-unit increase in SR magnitude during the safe conditions following the aversive stimulus, there was a 2.53 to 2.91 times greater risk for an anxiety disorder onset per year. SRs during danger, the only condition during which the aversive stimulus was and could be administered, were not statistically significant predictors of the onset of anxiety disorders, even when limiting the analyses to the imminent phase of danger conditions. This finding is consistent with prior cross-sectional data which have shown that whereas anxious individuals show more elevated

startle reflexes than healthy controls to cues that signal safety, the groups do not differ significantly in their responses to explicit threat cues (e.g., Grillon & Morgan, 1999;

Grillon et al., 2009). Danger condition SRs may represent the “strong situation” effect (Lissek, Pine, & Grillon, 2006), when anyone would be expected to show neurobiologically imperative fear responses.

The significant prediction of anxiety disorder onset from safe condition responses corresponds with findings from fear conditioning studies, in which individuals with anxiety disorders and those at risk for anxiety disorders show elevated fear responding to safe cues (i.e., CS−, Lissek et al., 2005; Lissek et al., 2009; Craske et al., 2008). As noted, the fear conditioning findings have been interpreted as deficits in inhibition of fear responses (Davis et al., 2000; Lissek et al., 2005). Thus, deficits in inhibitory mechanisms may help explain the current findings in our fear potentiation protocol. However, our study differs from fear conditioning studies in a number of ways, including the fact that fear conditioning studies do not directly compare responses to a series of safe (CS−) and potential danger (CS+) cues from before the delivery of an aversive stimulus (US) to after delivery of an aversive stimulus. In our study, the prediction of anxiety disorder onset was found only for safe conditions following delivery of the aversive stimulus. It is difficult to determine the precise mechanism accounting for this effect. One possibility is that safe conditions became ambiguous after the aversive muscle contraction for anxiety-prone participants, who therefore maintained more elevated defensive responding than did nonanxiety prone individuals. This account would accord with numerous studies showing that anxious individuals relative to healthy controls show larger threat-based responses to ambiguous stimuli (see Craske & Waters, 2005, for a review). On the other hand, the effects of ambiguity should have been strongest prior to the delivery of the muscle contraction, when the nature of the contraction itself and the extent to which the differing conditions were in fact predictive of safety and danger were still unknown, and yet the effects observed were found in the safe conditions following the delivery of the contraction.

Another possibility is that anxiety-prone individuals experienced greater stimulus generalization from the danger to the safe conditions after the contraction was delivered, since greater generalization has been found in anxious patients within conditioning paradigms (Lissek et al., 2010). However, this evidence for stimulus generalization gradients involves relatively subtle differences in stimulus size, in contrast to the very distinctly different safe (green screen, and words “safe: no contraction will be given”) versus danger (red screen and words “danger: contraction may be given”) conditions in the current study. Thus, stimulus generalization may not fully account for the observed effects.

Given the alternating nature of the series of safe-danger sequences, another possibility is that the safe conditions represented carry over from the preceding danger condition, or became a signal for the subsequent danger condition. In either case, responding to the safe conditions may be a form of anticipatory anxiety, especially after delivery of the stimulation. Whether the effects are due to deficits in activation of inhibitory mechanisms, as suggested by the fear conditioning literature, ambiguity, stimulus generalization, or anticipatory anxiety, the results suggest that elevated responding to safe conditions following an aversive stimulus signifies significant risk for the development of anxiety disorders. Future research is needed to tease apart the mechanisms underlying this risk factor. Additionally, the findings encourage future research on prevention interventions to offset the development of anxiety disorders in individuals who are positive on this risk factor.

Our second main goal was to evaluate the degree to which modulated SRs predicted unipolar depressive disorders. Across the board, SRs were not statistically significant

predictors of depression onset, and the effects for anxiety disorders remained significant even after entering the presence of a unipolar depressive disorder, as well as composite neuroticism, as covariates. Not only does this study represent the first prospective examination of the degree to which modulation of the SR offers a marker of risk for anxiety disorders, but it is also the first to demonstrate that elevated responding to safe conditions following an aversive event represents a marker of risk that is unique to anxiety disorders relative to unipolar depressive disorders and relative to neuroticism. These data are therefore highly informative for the ongoing debate about commonalities versus differences between anxiety and depressive disorders (e.g., Craske, Rauch, et al., 2009).

Neuroticism is a shared feature of anxiety and depression, both cross-sectionally and as a predictor of the onset of either type of disorder (e.g., Krueger et al., 1996; Breslau et al., 1995) including in our own data (Zinbarg et al., in preparation). Thus, even if elevated startle responding to safe conditions following an aversive stimulus is construed as a facet of neuroticism, it appears to tap unique variance—which, by definition, is separable from the general factor of neuroticism (Claridge & Davis, 2001; Uliaszek et al., 2009)—that is specific to risk for anxiety disorders and has incremental validity above and beyond the general factor of neuroticism. If elevated startle responding to safe conditions following an aversive stimulus had not predicted anxiety disorders above and beyond the general factor of neuroticism, parsimony would dictate that this aspect of startle responding simply be considered as a manifestation of general neuroticism (see Uliaszek et al., 2009, for details on the importance of incremental validity for the identification of facets of a construct).

The limitations of this study include a modest sample size and a limited number of disorder onsets, which may have reduced our power. In other words, although the number of onsets exceeded what is expected from population statistics, probably because we overselected on the risk factor of neuroticism, the low absolute number of onsets may render our results vulnerable to influential data points. Thus, it will be important that future research tests whether these findings are replicable. The sample was too small to include gender as a factor. In our prior study of SR and neuroticism, some effects were restricted to males (Craske, Waters et al., 2009), whereas other studies of populations at risk for anxiety disorder found effects that were specific to females (Grillon, Dierker, et al.,1998). Clearly, future research should address gender differences in prospective designs. Another sample size limitation was that we did not have sufficient numbers to exclude participants with depression from the analysis of the prediction of anxiety disorder onset; instead, we evaluated prediction of anxiety disorder onset while covarying presence of depression. Even though our results were maintained after covarying depression, and SRs did not statistically predict the onset of depression onset, future studies with larger samples may exclude depression as a further test of specificity of effects to anxiety disorder onset. It is also possible that with a longer follow-up interval, SRs may have predicted the onset of depression. For example, the trend for smaller magnitude SRs in the postcontraction safe condition to predict the onset of depression (the opposite direction than was observed to predict anxiety disorders) may have the potential to become a significant finding with larger samples.

Our sample size created another limitation, which was our inability to evaluate effects across different anxiety disorders. Conceivably, impairments in inhibitory mechanisms are specific to the development of certain anxiety disorders over other anxiety disorders. Although variables found to differentiate disorder groups do not necessarily map onto variables that predict the onset of different disorders, a larger sample size might at least allow for a test of a differential predictive role of elevated startle responding to safe conditions following an aversive stimulus across the anxiety disorders, or comorbid anxiety and depression.

Another limitation was the only moderately intense and unpleasant nature of the aversive stimulus, at least according to subjective ratings. By using a standardized intensity for the muscle contraction stimulation, we did not capitalize on individual differences in perceived intensity and aversiveness of painful stimuli. With an individually tailored and more intense and unpleasant muscle contraction, different effects, such as effects for precontraction safe conditions, might have been observed. On the other hand, the intensity and aversiveness ratings were completed after the entire procedure, and given the preprocedure instructions of receiving up to three contractions of progressively increasing intensity, it may well be that the postratings were deflated as compared with the aversiveness of potential contractions throughout the procedure. Furthermore, when perceived intensity and aversiveness were added as covariates to the model, the SR indices remained significant predictors of anxiety disorder onset.

Also, future analyses should complement measures of the SR as an index of defensive emotional responding with measures of skin conductance to emotionally relevant stimuli as a measure of arousal. Furthermore, selection biases from participation rates might have impacted generalizability of the findings, although participants who participated in the startle experiment did not differ significantly from remaining participants in terms of age, gender, ethnicity, and neuroticism.

In sum, adolescents who showed larger SRs in safe conditions, following delivery of an aversive muscle contraction, were at significantly greater risk of subsequently developing an anxiety disorder. This specific modulation of SR remained a significant predictor of anxiety disorders even after entering the onset of a unipolar depressive disorder, neuroticism, and aversiveness of the contraction as covariates. These findings suggest that elevated responding to stimuli that should signal safety within an aversive context is a risk factor unique to first onset anxiety disorders relative to first onset depression. Future studies may consider evaluating the extent to which modulation of SRs indexes risk for the subsequent onset of anxiety disorders above and beyond, or in interaction with, other known risk factors.

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References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th. Author; Washington, DC: 1994.

Andrews G, Anstey K, Brodaty H, Issakidis C, Luscombe G. Recall of depressive episode 25 years previously. Psychological Medicine. 1999; 29:787–791. doi:10.1017/S0033291799008648. [PubMed: 10473305]

Baker AG, Mercier P, Gabel J, Baker PA. Contextual conditioning and the US preexposure effect in conditioned fear. Journal of Experimental Psychology: Animal Behavior Processes. 1981; 7:109–128. doi:10.1037/0097-7403.7.2.109. [PubMed: 7241051]

Breslau N, Davis GC, Andreski P. Risk factors for PTSD-related traumatic events: A prospective analysis. The American Journal of Psychiatry. 1995; 152:529–535. [PubMed: 7694900]

Brown TA, Campbell LA, Lehman CL, Grisham JR, Mancill RB. Current and lifetime comorbidity of the DSM-IV anxiety and mood disorders in a large clinical sample. Journal of Abnormal Psychology. 2001; 110:585–599. doi:10.1037/0021-843X.110.4.585. [PubMed: 11727948]

Carver CS, White TL. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS scales. Journal of Personality and Social Psychology. 1994; 67:319–333. doi:10.1037/0022-3514.67.2.319.

Claridge G, Davis C. What's the use of N? Personality and Individual Differences. 2001; 31:383–400. doi:10.1016/S0191-8869(00)00144-6.

Clark LA, Watson D, Mineka S. Temperament, personality, and the mood and anxiety disorders. Journal of Abnormal Psychology. 1994; 103:103–116. doi:10.1037/0021-843X.103.1.103. [PubMed: 8040472]

Craske MG, Rauch S, Ursano R, Prenoveau J, Pine D, Zinbarg R. What is an anxiety disorder? Depression and Anxiety. 2009; 26:1066–1085. doi:10.1002/da.20633. [PubMed: 19957279]

Craske MG, Waters AM, Nazarian M, Mineka S, Zinbarg RE, Griffith JW, Ornitz EM. Does neuroticism in adolescents moderate contextual and explicit threat cue modulation of the startle reflex? Biological Psychiatry. 2009; 65:220–226. doi:10.1016/j.biopsych.2008.07.020. [PubMed: 18789433]

Craske MG, Waters AM. Panic disorder, phobias, and generalized anxiety disorder. Annual Review of Clinical Psychology. 2005; 1:197–225. doi:10.1146/annurev.clinpsy.1.102803.143857.

Craske MG, Waters AM, Bergman L, Naliboff B, Lipp OV, Negoro H, Ornitz EM. Is aversive learning a marker of risk for anxiety disorders in children? Behaviour Research and Therapy. 2008; 46:954–967. doi:10.1016/j.brat.2008.04.011. [PubMed: 18539262]

Davis, M.; Falls, WA.; Gewirtz, J. Neural systems involved in fear inhibition: Extinction and conditioned inhibition. In: Myslobodsky, MS.; Weiner, I., editors. Contemporary issues in modeling psychopathology . Kluwer Academic/Plenum Publishers; New York, NY: 2000. p. 113-141.

Di Nardo, PA.; & Barlow, DH. Anxiety Disorders Interview Schedule-Reivsed (ADIS-R). Graywind Publications; Albany, NY: 1988.

Eysenck, H.; Eysenck, S. Manual of the Eysenck Personality Questionnaire. Hodder & Stoughton; London, UK: 1975.

First, M.; Gibbon, M.; Spitzer, R.; Williams, J. Structured clinical interview for DSM-IV-TR Axis I Disorders (SCID-I), research version. Biometrics Research Department, New York State Psychiatric Institute; New York, NY: 2002.

Gracely RH, McGrath P, Dubner R. Validity and sensitivity of ratio scales of sensory and affective verbal pain descriptors: Manipulation of affect by diazepam. Pain. 1978; 5:19–29. doi: 10.1016/0304-3959(78)90021-0. [PubMed: 673439]

Grillon C, Ameli R. Effects of threat of shock, shock electrode placement and darkness on startle. International Journal of Psychophysiology. 1998; 28:223–231. doi:10.1016/S0167-8760(97)00072-X. [PubMed: 9545658]

Grillon C, Ameli R, Foot M, Davis M. Fear-potentiated startle: Relationship to the level of state/trait anxiety in healthy subjects. Biological Psychiatry. 1993; 33:566–574. doi: 10.1016/0006-3223(93)90094-T. [PubMed: 8329489]

Grillon C, Ameli R, Goddard A, Woods SW, Davis M. Baseline and fear-potentiated startle in PD patients. Biological Psychiatry. 1994; 35:431–439. doi:10.1016/0006-3223(94)90040-X. [PubMed: 8018793]

Grillon C, Dierker L, Merikangas K. Fear-potentiated startle in adolescent offspring of parents with anxiety disorders. Biological Psychiatry. 1998; 44:990–997. doi:10.1016/S0006-3223(98)00188-7. [PubMed: 9821563]

Grillon C, Morgan C III. Fear-potentiated startle conditioning to explicit and contextual cues in Gulf War veterans with posttraumatic stress disorder. Journal of Abnormal Psychology. 1999; 108:134–142. doi:10.1037/0021-843X.108.1.134. [PubMed: 10066999]

Grillon C, Morgan C III, Davis M, Southwick S. Effects of experimental context and explicit threat cues on acoustic startle in Vietnam veterans with posttraumatic stress disorder. Biological Psychiatry. 1998; 44:1027–1036. doi:10.1016/S0006-3223(98)00034-1. [PubMed: 9821567]

Grillon C, Pine DS, Lissek S, Rabin S, Bonne O, Vythilingam M. Increased anxiety during anticipation of aversive unpredictable stimuli in post-traumatic stress disorder but not in

generalized anxiety disorder. Biological Psychiatry. 2009; 66:47–53. doi:10.1016/j.biopsych.2008.12.028. [PubMed: 19217076]

Grillon C, Warner V, Hille J, Merikangas KR, Bruder GE, Tenke CE, Weissman MM. Families at high and low risk for depression: A three-generation startle study. Biological Psychiatry. 2005; 57:953–960. doi:10.1016/j.biopsych.2005.01.045. [PubMed: 15860334]

Hayward C, Killen J, Kraemer H, Taylor C. Predictors of panic attacks in adolescence. Journal of the American Academy of Child & Adolescent Psychiatry. 2000; 39:207–214. doi:10.1097/00004583-200002000-00021. [PubMed: 10673832]

Heft MW, Gracely RH, Dubner R, McGrath PA. A validation model for verbal description scaling of human clinical pain. Pain. 1980; 9:363–373. doi:10.1016/0304-3959(80)90050-0. [PubMed: 7208081]

Kessler RC, Chiu WC, Demier O, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey-Replication. Archives of General Psychiatry. 2005; 62:617–627. doi:10.1001/archpsyc.62.6.617. [PubMed: 15939839]

Krueger RF, Caspi A, Moffitt T, Silva P, McGee R. Personality traits are differentially linked to mental disorders: A multitrait-multidiagnosis study of an adolescent birth cohort. Journal of Abnormal Psychology. 1996; 105:299–312. doi:10.1037/0021-843X.105.3.299. [PubMed: 8772001]

Krueger RF. The structure of common mental disorders. Archives of General Psychiatry. 1999; 56:921–926. doi:10.1001/archpsyc.56.10.921. [PubMed: 10530634]

Lang PJ, McTeague LM. The anxiety disorder spectrum: Fear imagery, physiological reactivity, and differential diagnosis. Anxiety, Stress, & Coping: An International Journal. 2009; 22:5–25. doi:10.1080/10615800802478247.

Lau JY, Lissek S, Nelson EE, Lee Y, Roberson-Nay R, Poeth K, Pine DS. Fear conditioning in adolescents with anxiety disorders: Results from a novel experimental paradigm. Journal of the American Academy of Child & Adolescent Psychiatry. 2008; 47:94–102. doi:10.1097/chi.0b01e31815a5f01. [PubMed: 18174830]

Lissek S, Pine D, Grillon C. The strong situation: A potential impediment to studying the psychobiology and pharmacology of anxiety disorders. Biological Psychology. 2006; 72:265–270. doi:10.1016/j.biopsycho.2005.11.004. [PubMed: 16343731]

Lissek S, Powers AS, McClure EB, Phelps EA, Woldehawariat G, Grillon C, Pine DS. Classical fear conditioning in the anxiety disorders: A meta-analysis. Behaviour Research and Therapy. 2005; 43:1391–1424. doi:10.1016/j.brat.2004.10.007. [PubMed: 15885654]

Lissek S, Rabin S, Heller RE, Lukenbaugh DE, Pine DS, Grillon C. Overgeneralization of conditioned fear as a pathogenic marker of panic disorder. The American Journal of Psychiatry. 2010; 167:47–55. doi:10.1176/appi.ajp.2009.09030410. [PubMed: 19917595]

Lissek S, Rabin S, McDowell DJ, Dvir S, Bradford DE, Geraci M, Grillon C. Impaired discriminative fear conditioning resulting from elevated fear responding to learned safety cues among individuals with panic disorder. Behaviour Research and Therapy. 2009; 47:111–118. doi:10.1016/j.brat.2008.10.017. [PubMed: 19027893]

Melzig CA, Weike AI, Zimmermann J, Hamm AO. Startle reflex modulation and autonomic responding during anxious apprehension in PD patients. Psychophysiology. 2007; 44:846–854. doi:10.1111/j.1469-8986.2007.00560.x. [PubMed: 17640268]

Mineka S, Watson D, Clark LA. Cormorbidity of anxiety and unipolar mood disorders. Annual Review of Psychology. 1998; 49:377–412. doi:10.1146/annurev.psych.49.1.377.

Mor N, Zinbarg RE, Craske MG, Mineka S, Uliaszek A, Rose R, Waters AM. Evaluating the invariance of the factor structure of the EPQ-R-N among adolescents. Journal of Personality Assessment. 2008; 90:66–75. doi:10.1080/00223890701693777. [PubMed: 18444097]

Naliboff BD, Waters AM, Labus JS, Kilpatrick L, Craske MG, Chang L, Ornitz E. Increased acoustic startle responses in IBS patients during abdominal and nonabdominal threat. Psychosomatic Medicine. 2008; 70:920–927. doi:10.1097/PSY.0b013e318186d858. [PubMed: 18842745]

Neumann DL, Waters AM. The use of an unpleasant sound as an unconditional stimulus in a human Pavlovian conditioning procedure. Biological Psychology. 2006; 73:175–185. doi:10.1016/j.biopsycho.2006.03.004. [PubMed: 16698165]

Pole N, Neylan TC, Best SR, Orr SP, Marmar CR. Fear-potentiated startle and posttraumatic stress symptoms in urban police officers. Journal of Traumatic Stress. 2003; 16:471–479. doi:10.1023/A:1025758411370. [PubMed: 14584631]

Reeb–Sutherland BC, Helfinstein SM, Degnan KA, Perez-Edgar K, Henderson HA, Lissek S, Fox NA. Startle response in behaviorally inhibited adolescents with a lifetime occurrence of anxiety disorders. Journal of the American Academy of Child & Adolescent Psychiatry. 2009; 48:610–617. doi:10.1097/CHI.0b013e31819f70fb. [PubMed: 19454917]

Saucier G. Mini-Markers: A brief version of Goldberg's unipolar Big-Five markers. Journal of Personality Assessment. 1994; 63:506–516. doi:10.1207/s15327752jpa6303_8. [PubMed: 7844738]

Singer, J.; Willett, J. Applied longitudinal data analysis: Modeling change and event occurrence. Oxford University Press; New York, NY: 2003.

Twiss C, Kilpatrick L, Craske MG, Buffington CA, Ornitz E, Rodriguez LV, Naliboff BD. Increased startle responses in interstitial cystitis: Evidence for central hyperresponsiveness to visceral related threat. Journal of Urology. 2009; 181:2127–2133. doi:10.1016/j.juro.2009.01.025. [PubMed: 19286199]

Uliaszek AA, Hauner KK, Zinbarg RE, Craske MG, Mineka S, Griffith JW, Rose RD. An examination of content overlap and disorder-specific predictions in the associations of neuroticism with anxiety and depression. Journal of Research in Personality. 2009; 43:785–794. doi:10.1016/j.jrp.2009.05.009. [PubMed: 20161016]

Waters AM, Henry J, Neumann DL. Aversive Pavlovian conditioning in childhood anxiety disorders: Impaired response inhibition and resistance to extinction. Journal of Abnormal Psychology. 2009; 118:311–321. doi:10.1037/a0015635. [PubMed: 19413406]

Waters AM, Neumann DL, Henry J, Craske MG, Ortnitz EM. Baseline and affective startle modulation by angry and neutral faces in 4–8-year-old anxious and non-anxious children. Biological Psychology. 2008; 78:10–19. doi:10.1016/j.biopsycho.2007.12.005. [PubMed: 18243481]

Watson D. Re-thinking the mood and anxiety disorders: A quantitative hierarchical model for DSM-V. Journal of Abnormal Psychology. 2005; 114:522–536. doi:10.1037/0021-843X.114.4.522. [PubMed: 16351375]

Yamada F, Yamasaki K, Nakayama M, Miyata Y. Distribution of eyeblink amplitude recorded by an electrode hookup: Reexamination. Perceptual and Motor Skills. 1980; 51:1283–1287. doi:10.2466/pms.1980.51.3f.1283. [PubMed: 7220231]

Zinbarg RE, Mineka S, Craske MG, Griffith JW, Sutton J, Rose RD, Waters AM. The Northwestern-UCLA youth emotion project: Associations of cognitive vulnerabilities, neuroticism and gender with past diagnoses of emotional disorders in adolescents. Behaviour Research and Therapy. 2010; 48:347–358. doi:10.1016/j.brat.2009.12.008. [PubMed: 20070951]

Zinbarg, R.; Mineka, S.; Craske, M.; Griffith, J.; Vrshek-Schallhorn, S.; Wolitzy–Taylor, KB.; Epstein, A. Prospective associations of personality traits and cognitive vulnerabilities with diagnoses of emotional disorders over three years in adolescents. in preparation

Table 1

Means (SEs) of SR Magnitudes (Ln-Transformed μV) for Baseline and for Safe and Danger Conditions, Pre- and Postcontraction, Across Entire Sample

Phase	Mean (*SE*)
Baseline	4.25 (0.95)
Precontraction safe	4.08 (0.04)
Precontraction danger	4.29 (0.05)
Postcontraction safe	3.78 (0.04)
Postcontraction danger	4.12 (0.06)
Danger	
Precontraction preimminent	4.23 (0.04)
Precontraction imminent	4.71 (0.04)
Postcontraction preimminent	4.01 (0.04)
Postcontraction imminent	4.71 (0.04)

Note. Mean (*SE*) of all safe and danger variables adjusted for baseline. Mean (*SD*) for baseline.

Table 2

Frequencies of Anxiety and Unipolar Depressive Disorders

a) First onsets across time points (cases censored for Cox regression; *N* = 132)				
	Year 1	**Year 2**	**Year 3**	**Year 4**
Anxiety	4 (3.0%)	5 (3.8%)	4 (3.0%)	3 (2.3%)
	M = 1	M = 2	M = 2	M = 2
Depression	11 (8.3%)	9 (6.8%)	8 (6.0%)	6 (4.5%) M = 1
	M = 4	M = 4	M = 1	M = 1

b) Number in sample (including censored cases)	
Panic disorder	4
Social phobia	5
Specific phobia	1
Obsessive compulsive disorder	3
Generalized anxiety disorder	1
*Anxiety disorder NOS	2
Major depressive disorder	20
Dysthymia	1
Adjustment disorder	6
**Unipolar depression NOS	7

Note. a) Year 0 (baseline) assessment not included in longitudinal analyses. Anxiety = anxiety disorder diagnosis; depression = unipolar depressive disorder diagnosis; M = males; NOS = not otherwise specified. This table reports the number of cases counted in Cox regression at each time point (i.e., after censoring cases). Cases were censored from subsequent time points once an onset occurred.

b)

*One anxiety disorder NOS case had posttraumatic stress disorder symptoms, with insufficient symptoms for criteria C and D to reach threshold for a diagnosis. The other anxiety disorder NOS case had panic disorder symptoms and did not meet criteria for the disorder due to having limited symptom panic attacks (i.e., three, instead of four, panic attack symptoms) and not fully meeting criterion A(2).

**Among the unipolar depressive disorder NOS cases, five had major depressive disorder symptoms and two had minor depressive disorder symptoms. In all but one case, participants met for depressed mood and had one to three additional symptoms; in one case, the participants did not fully meet for depressed mood and/or anhedonia (both symptoms scored as subthreshold); and in two cases, symptoms only lasted for 1 week. There were only two participants with onsets of an anxiety disorder and unipolar depression in the same year.

Table 3

Means (SDs) of SR Magnitudes Disorder Onset and Depression (in Ln-Transformed Disorder versus No Deprer Safe and Danger Con ssion Disorder Onset ditions by Anxiety Dis order versus No Anxiety

Variable	Anxiety disorder	vs.	No anxiety disorder	Depression disorder	vs.	No depression disorder
Baseline	4.04 (1.09)		4.27 (0.93)	4.27 (1.08)		4.23 (0.91)
Safe condition precontraction	3.93 (0.91)		4.07 (0.88)	4.02 (1.05)		4.06 (0.83)
Safe condition postcontraction	3.86 (0.91)		3.74 (0.96)	3.84 (1.02)		3.73 (0.93)
Danger condition precontraction	4.14 (0.94)		4.31 (0.82)	4.30 (0.94)		4.28 (0.80)
Danger condition postcontraction	3.98 (0.93)		4.12 (0.89)	4.14 (0.85)		4.09 (0.91)
Danger condition						
Preimminent precontraction	4.10 (0.80)		4.23 (0.80)	4.24 (0.89)		4.18 (0.80)
Imminent precontraction	4.56 (0.88)		4.73 (0.79)	4.86 (0.66)		4.66 (0.83)
Preimminent postcontraction	3.86 (0.88)		4.03 (0.83)	3.98 (0.88)		3.99 (0.87)
Imminent postcontraction	4.48 (0.96)		4.72 (0.75)	4.74 (0.72)		4.68 (0.80)

Table 4

Hazard Ratios and Confidence Intervals for Models Predicting Anxiety Disorder Onset

Predictor	HR	*p*-value	95% CIs
Safe condition SR precontraction	1.43	.56	0.20–1.67
Safe condition SR postcontraction	2.53	<.05	1.11–5.83
Danger condition SR precontraction	1.24	.74	0.36–4.23
Danger condition SR postcontraction	1.07	.91	0.34–3.31
Danger condition SR preimminent precontraction	1.24	.75	0.34–4.47
Danger condition SR imminent precontraction	0.84	.72	0.33–2.13
Danger condition SR preimminent postcontraction	0.85	.82	0.22–3.28
Danger condition SR imminent postcontraction	0.44	.19	0.13–1.52

Note. SR = startle response; HR = hazard ratio; 95% CIs = 95% confidence intervals. Shading indicates statistically significant predictors of anxiety disorders.

Table 5

Hazard Ratios and Confidence Intervals for Models Predicting Depressive Disorder Onset

Predictor	HR	*p*-value	95% CIs
Safe condition SR precontraction	0.72	.44	0.31–1.66
Safe condition SR postcontraction	1.45	.19	0.84–2.50
Danger condition SR precontraction	1.05	.91	0.44–2.54
Danger condition SR postcontraction	1.05	.91	0.48–2.31
Danger condition SR preimminent precontraction	1.02	.97	0.43–2.43
Danger condition SR imminent precontraction	1.75	.09	0.91–3.37
Danger condition SR preimminent postcontraction	0.62	.29	0.26–1.50
Danger condition SR imminent postcontraction	0.76	.51	0.34–1.70

Note. SR = startle response; HR = hazard ratio; 95% CIs = 95% confidence interval.