HHS Public Access

Author manuscript

Behav Res Ther. Author manuscript; available in PMC 2016 January 19.

Published in final edited form as:

Behav Res Ther. 2008 August ; 46(8): 954–967. doi:10.1016/j.brat.2008.04.011.

Is aversive learning a marker of risk for anxiety disorders in children?

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Abstract

Aversive conditioning and extinction were evaluated in children with anxiety disorders (n = 23), at-risk for anxiety disorders (n = 15), and controls (n = 11). Participants underwent 16 trials of discriminative conditioning of two geometric figures, with (CS+) or without (CS−) an aversive tone (US), followed by 8 extinction trials (4 CS+, 4 CS−), and 8 extinction re-test trials averaging 2 weeks later. Skin conductance responses and verbal ratings of valence and arousal to the CS +/CS− stimuli were measured. Anxiety disordered children showed larger anticipatory and unconditional skin conductance responses across conditioning, and larger orienting and anticipatory skin conductance responses across extinction and extinction re-test, all to the CS+ and CS−, relative to controls. At-risk children showed larger unconditional responses during conditioning, larger orienting responses during the first block of extinction, and larger anticipatory responses during extinction re-test, all to the CS+ and CS−, relative to controls. Also, anxiety disordered children rated the CS+ as more unpleasant than the other groups. Elevated skin conductance responses to signals of threat (CS+) and signals of safety (CS−; CS+ during extinction) are discussed as features of manifestation of and risk for anxiety in children, compared to the specificity of valence judgments to the manifestation of anxiety.

Keywords

Children; Anxiety disorders; At-risk; Conditioning; Extinction; Skin conductance

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Introduction

The goal of the current study was to evaluate characteristics of aversive conditioning that may identify the risk for anxiety disorders in children. Childhood and adolescent anxiety disorders are common, with estimates ranging from 5.3% to 17% (see Cartwright-Hatton, McNicol, & Doubleday, 2006, for a review). Also, childhood anxiety poses a risk for adolescent anxiety, which poses an even greater risk for adulthood anxiety and depression (Pine, Cohen, Gurley, Brook, & Ma, 1998). In addition to emotional costs, anxiety disorders in children and adolescents are associated with academic and vocational underachievement (Kessler, Foster, Saunders, & Slang, 1995) and impaired social competence (Spence, Donovan, & Brechman-Toussaint, 1999). Investigation of children at-risk may enhance our understanding of the etiology of this common and costly set of childhood disorders, and inform the development of prevention efforts.

Risk factors for childhood anxiety disorders include multiple fears and persistent anxiety symptoms (Muris, Merckelbach, Mayer, & Prins, 2000), and temperamental traits of neuroticism and behavioral inhibition (Hayward, Killen, Kraemer, & Taylor, 1998; Schwartz, Snidman, & Kagan, 1999). Parental anxiety is another risk factor, as offspring of parents with anxiety disorders are at 3.5 (range 1.3–13.3) times greater the risk for anxiety disorders than are offspring of control parents (e.g., Merikangas, Avenevoli, Dierker, & Grillon, 1999).

Risk factors themselves do not illuminate mechanisms or pathways by which risk is conferred (e.g., Ormel, Rosmalen, & Farmer, 2004). One such mechanism may be the strength of aversive conditioned responses and their persistence over time. Fear conditioning has long been implicated in the etiology of phobias and anxiety disorders (see Eelen & Vervliet, 2006; Field, 2006). Interest in fear conditioning and extinction has been revived by advances in the basic science of their underlying neurobiology (see Myers & Davis, 2007). Also, etiological models of anxiety disorders recognize the moderating role of individual difference variables (such as ones that place children at-risk for anxiety disorders) upon aversive conditioning (Mineka & Zinbarg, 2006; Ohman & Mineka, 2001).

There is now good evidence for larger conditioned responding during conditioning and more sustained responding during extinction trials in anxiety disordered *adult* samples relative to controls (Lissek et al., 2005). These effects have been measured mostly using skin conductance responses (SCR), an index of changes in general arousal associated with emotional states (Cacioppo, Berntson, Larsen, Poehlmann, & Ito, 2000), and attentional processes associated with the orienting reflex (e.g., Gray & McNaughton, 2000). These effects are most evident in single cue conditioning (i.e., a single conditional stimulus [CS] is paired with an unconditional stimulus [US]) rather than in discrimination conditioning paradigms (i.e., one CS is paired with the US [CS+] and a second is presented alone [CS−]) (Lissek et al., 2005). In discrimination paradigms, anxiety disordered samples typically (but not always) show elevated SCRs to both the CS+ and the CS− during conditioning and extinction compared to controls (e.g., Grillon & Morgan, 1999; Orr et al., 2000; Peri, Ben-Shakhar, Orr, & Shalev, 2000; Veit et al., 2002). Within an associative model, these findings have been interpreted as anxiety disordered individuals displaying elevated fear responding

to excitatory cues (CS+ trials) as well as impaired inhibition of fear responding to safety cues (CS− and extinction trials) (Davis, Falls, & Gewirtz, 2000) and overgeneralization from the CS+ to the CS− due to failure to discriminate the stimulus features that distinguish threat from safety cues (see Lissek et al., 2005, for a review). Non-associative explanations of elevated responding to both CS+ and CS− primarily focus on sensitization, or elevated responsiveness to the US and other novel stimuli due to elevated anxious state, and habituation, or decreased responding over repeated presentations of specific stimuli (Lissek et al., 2005).

Only one published study to date has investigated aversive conditioning in anxiety disordered children. Specifically, Liberman, Lipp, Spence, and March (2006) found that both anxiety disordered children and non-anxious controls failed to discriminate between CS + and CS− trials during acquisition, as indexed by the magnitude of SCRs. However, during extinction, the anxiety disordered group showed larger SCRs (reflecting arousal) as well as larger startle eye blink reflexes (a measure of emotional valence; Lissek et al., 2005) during CS+ than CS− trials. Even though there has been no investigation of these characteristics in children at-risk for anxiety disorders, there is evidence that individual difference variables associated with risk for anxiety disorders moderate aversive conditioning. That is, in unselected samples, more sympathetically aroused individuals show larger SCRs to the CS+ in simple conditioning (Ohman & Bohlin, 1973) and larger SCRs to both the CS+ and CS− during discriminative conditioning and resistance to extinction (Hugdahl, Fredrikson, & Ohman, 1977). Also, traits of anxiety (Spence & Spence, 1966) have been associated with stronger eyelid conditioning, as have traits of anxiety with aversive expectations for avoidance cues (Zinbarg & Mohlman, 1998). Even though the results with trait anxiety are not always consistent (e.g., Guimaraes, Hellewell, Hensman, & Wang, 1991), the combined data pertaining to individual difference variables lends credence to the hypothesis that children at-risk for anxiety disorders may exhibit patterns of conditioning and extinction different from control children.

The goal of this study was to evaluate discrimination conditioning and extinction effects as a potential mechanism by which risk for anxiety disorders is conferred. Rather than selecting children who are at-risk based on their presenting features (such as temperament), we selected children at-risk by virtue of their parental diagnostic status. By so doing, we avoided the tautology of assessing mechanisms of risk in children selected for their manifestation of risk, and capitalized on the reduced heterogeneity inherent to a family study approach (Merikangas et al., 1999). We hypothesized that anxiety disordered children and children at-risk for anxiety disorders would show larger SCRs to the CS+ and the CS− during discrimination conditioning, and larger SCRs to the CS+ during extinction, relative to non-anxious control children. Also, we hypothesized parallel findings in verbal ratings of valence and arousal.

Method

Participants

Participants (Ps) were 49 children (26 boys; 23 girls), aged between 7 years and 12 years, 9 months (M = 9.42 years; SD = 1.62). At-risk children were recruited from parents attending

the UCLA Anxiety Disorders Behavioral Research Program, and from advertisements within the local community and elementary schools in the Los Angeles area (with school district approvals). Anxious and non-anxious control children were recruited through the local community and elementary schools. All children were the biological offspring of their parents.

Children were assessed using the Anxiety Disorders Interview Schedule for DSM-IV—Child version (ADIS-C-IV; Silverman & Albano, 1996). Parents were assessed with the lifetime version of the ADIS (ADIS-IV-L; Brown, DiNardo, & Barlow, 1994). In both schedules, interviewers assign a 0–8 point clinical severity rating (CSR) for each diagnosis, indicating level of distress/disablement, with ratings of 4 or more representing clinical severity. Children and parents were deemed to have an anxiety disorder if they met DSM-IV criteria for an anxiety disorder with a CSR of 4 or greater.

Anxious group

Children met criteria for a principal (i.e., highest CSR) anxiety disorder diagnosis of separation anxiety disorder (SAD), panic disorder (PD), generalized anxiety disorder (GAD), or social anxiety disorder (SOC) with a CSR of 4 or greater, or specific phobia (SP) with a CSR of 4 or greater if accompanied by another anxiety disorder diagnosis with a CSR of 3 or greater.[1] Parental anxiety status was not taken into account. To reduce sample heterogeneity, children were excluded if their *principal* anxiety diagnosis was either obsessive compulsive disorder or posttraumatic stress disorder. Of the 23 ANX children (11 boys; 12 girls), 9 had a principal diagnosis of GAD (mean CSR = 4.25), 6 had SOC (mean CSR = 5.2), 4 had SAD (mean CSR = 5), and 4 had SP (mean CSR = 4.4).

At-risk group

Either or both biological parents met criteria for a current or past anxiety disorder (beyond the age of 10) with a CSR of 4 or greater, whereas the child neither met criteria for any anxiety disorder nor exhibited subclinical anxiety symptoms with a CSR greater than 2, current or past. We elected either biological parent given the evidence that paternal anxiety confers the same risk as maternal anxiety (e.g., Connell & Goodman, 2002). We excluded families in whom parental anxiety did not extend beyond the age of 10 as a way of setting a minimal level of parental risk and ensuring that the parental anxiety disorder was not a transient anxiety state during childhood. On the other hand, parental anxiety disorders were not required to persist throughout the life of the participating child, because patterns of familial aggregation, being at least partly explained by additive genetic factors (Kendler, Neale, Kessler, Heath, & Eaves, 1992), are not solely reliant upon parental ‘behavioral expression’. At least one parent (14 mothers and 4 fathers) was directly interviewed. The 15 AR children (9 boys; 6 girls) did not meet criteria for any psychiatric disorder. Of these children, 7 had a mother with a current anxiety disorder (4 with GAD (mean CSR = 4.5), 2 with SP (mean CSR = 4.5), and 1 with SOC (CSR = 5) and one had a father with a current SP (CSR = 5). Four had mothers with a past anxiety disorder: 2 with GAD (mean CSR =

[1]Those with a principal diagnosis of specific phobia were required to have an additional diagnosis of another anxiety disorder with a CSR of at least 3 to ensure that they were sufficiently anxious, since circumscribed specific phobias can sometimes be associated with less general anxiety than other anxiety disorders (e.g., Craske & Waters, 2005).

4.5), 1 with SOC (CSR = 4) and 1 with SP (CSR = 4). One had a father with past PD (CSR = 4). Two cases in which the mother and/or father met criteria for three or more anxiety disorders with CSRs of 3 were included because they also met criteria for major depressive disorder with CSRs of 4 and 6; parental depression is another risk factor for childhood anxiety (Biederman et al., 2001).

Control group

For the 11 children assigned to the control (CON) group (6 boys; 5 girls), neither the child nor either biological parent met criteria for an anxiety disorder nor received a CSR greater than 2 for symptoms of anxiety, current or past, with the exception of parental anxiety disorders that did not continue beyond the age of 10 years (n = 1). All mothers were directly interviewed whereas 6 fathers were not interviewed and their history of anxiety and mood disorders was gleaned from the mother.

Children were excluded from all groups if they had chronic medical conditions (e.g., severe asthma, diabetes, sickle cell anemia and juvenile rheumatoid arthritis), intellectual impairment, pervasive developmental disorders, bipolar disorder, organic brain damage, or psychoses. Children with attention deficit hyperactivity disorder (ADHD) were not excluded, given that prior research has shown that 6–12 year olds with ADHD do not differ from controls in terms of discrimination conditioning and extinction (Pliszka, Hatch, Borcherding, & Rogeness, 1993). Medications that may influence autonomic and/or endocrine functioning were reason for exclusion if taken within 2 weeks of the laboratory visits. Children taking psychotropic medications for any reason were excluded.

The three groups did not differ on demographic variables: age, $F(2, 46) = .71$, $p = .93$, gender, $\chi^2(2) = .55$, $p = .76$, ethnicity, $\chi^2(2) = 3.97$, $p = .14$ (63% Caucasian, 37% other), or public vs private schooling of children, $\chi^2(2) = .93$, $p = .65$ (84% public schools; 16% private schools). There also were no differences in parental marital status, $\chi^2(2) = 1.43$, $p = .49$ (68% married, 32% other), annual family income, $\chi^2(2) = 2.44$, $p = .30$, (59% with $60,001 or more; 41% with less than $60,000), or level of educational attainment of fathers, $\chi^2(2) = 3.61$, $p = .16$ (70% with college or postgraduate graduation; 30% with other type of educational attainment) or mothers, $\chi^2(2) = 3.87$, $p = .14$ (65% with college or postgraduate graduation; 35% with other type of educational attainment).

Overall design

The three groups of children (ANX, AR, and CON) completed a discrimination conditioning paradigm, followed immediately by an extinction paradigm. After an interval averaging almost 2 weeks, Ps completed an extinction re-test paradigm to provide a sensitive index of extinction learning (Rescorla, 2006).

Materials and apparatus

The Anxiety Disorders Interview Schedule for Children, Version IV—(ADIS-C-IV; Silverman & Albano, 1996). The ADIS-C-IV is a semi-structured diagnostic interview that assesses the major DSM-IV anxiety, mood, and externalizing disorders in school-aged children and adolescents, with favorable psychometric properties (Silverman, Saavedra, &

Pina, 2001; Wood, Piacentini, Bergman, McCracken, & Barrios, 2002). The ADIS-C-IV was completed with parents and children together (as is done in other studies, e.g., Pediatric OCD Treatment Study (POTS) Team, 2004) by postdoctoral and doctoral researchers who had undergone specialized training in the ADIS-C-IV according to procedures recommended by the developers (A.M. Albano, personal communication 1999). All ADIS-C-IV interviews were reviewed by the research team. Kappa coefficients between the interviewer and research team consensus, for each diagnosis with sufficient numbers, were as follows: SOC-.89; SP-.92; GAD-.84; and SAD—1.0. Corresponding Pearson correlation coefficients for CSR ratings were .98, .86, .88 and .82, respectively.

The Anxiety Disorders Interview Schedule for DSM-IV, Adult version-Lifetime —(ADIS-IV-L; Brown et al., 1994) is a semi-structured interview that assesses current and past (i.e., lifetime) episodes of DSM-IV anxiety, mood, somatoform, and substance use disorders, with sound psychometric properties (Brown et al., 1994). The ADIS-IV was administered in person to the attendant parent (mostly mothers) and by phone to the non-attending parent. When the non-attending parent was unavailable, the attending parent was asked whether the non-attending parent (8 mothers and 39 fathers) had ever had significant problems with anxiety or depression or been treated for these disorders. The ADIS-IV-L was administered by postdoctoral and doctoral researchers who had previously demonstrated reliability. All ADIS-IV-L interviews were reviewed by the research team. Kappa coefficients between the interviewer and research team consensus, for each maternal diagnosis with sufficient numbers, were as follows: SOC—.93; SP—.96; and GAD-.93. Corresponding Pearson correlation coefficients for CSR ratings were .97, .98, and .90, respectively.

The Multidimensional Anxiety Scale for Children (MASC) (parent and child versions)—*(March 1998)* is a standardized 39-item self-report measure of anxiety, with a 4-point Likert-type response scale ranging from never true about me (0) to often true about me (3). The child version was accompanied by parent report version containing identical items. March, Parker, Sullivan, Stallings, and Connors (1997) found modest to moderate agreement between parent and child versions, and subsequent investigations using a parent version have found further psychometric support (Langley, Bergman, & McCracken, 2004; Wood et al., 2002).

The Children's Depression Inventory—(*CDI*; Kovacs, 1985) is a 27-item questionnaire with a 3-point response scale. This scale yields a total *T* score, indicating the severity of depressed mood. Acceptable psychometrics have been reported for this measure (e.g., Kovacs, 1981).

Verbal ratings

Ps rated four geometric figures, including the CS+ (trapezoid) and CS− (triangle) and two additional figures (circle and rectangle), prior to and following conditioning, following extinction, and prior to and following extinction re-test. Ratings were made using a Self Assessment Manikin (SAM) that depicted cartoon-like figures along two-tail, 5-point scales of Valence (unpleasant-pleasant) and Arousal (calm-worked up) (CSEA-NIMH, 1999), with

higher scores reflecting that the shapes made Ps feel more pleasant valence and greater perceived arousal. Specifically, Ps were instructed as follows: “SAM is this little guy. On the top line, SAM looks happy at this end, in the middle he looks blank or calm, and at this end he looks unhappy. See how he is smiling and happy at this end, and not smiling and unhappy at this end. So I want you to tell me how happy to unhappy the shape makes you feel by placing a cross through one of these pictures of SAM. You should only put a cross through one picture on this line. On this next line, at this end, SAM is all worked up in the tummy. See how his tummy is all worked up. Down this end, SAM is calm and relaxed. See how his tummy is calm. So for each shape, I want you to also tell me how worked up the shape makes you feel by putting a cross through one of these pictures of SAM. You should only put a cross through one picture on this line.”

Contingency awareness

Following conditioning, Ps were asked “Did you happen to notice whether the tone you heard came on during one of the shapes?” If they answered “Yes” they were asked to indicate “which shape did it come on during?”

Electrophysiological materials and equipment

The US was a 1 s, 1000Hz pure tone set at 107 dB delivered through Sony stereophonic headphones. The CS+ and CS− were geometric shapes (8.5 cm wide and 10.5 cm high); a pastel pink trapezoid and a pastel cream triangle, each presented for 8 s at a distance of 6.5cm either to the right or left of a central fixation cross on equal numbers of trials. They were presented on a Dell 21” color monitor at a distance of 1m, at a visual angle that averaged 9.6 degrees.

Trial-by-trial conditioned responding to the CS+ and CS− was measured by SCRs, recorded from two Ag/AgCl electrodes (Grass, F-E9M-60-5) placed on the distal phalanx of the index and middle fingers of the non-dominant hand and a ground electrode placed in the center of the forehead. The impedance level of electrodes was 15 kΩ or less. SCR data were acquired using a Grass Instruments Amplifier System (Model 15RXI) and were digitized and sampled on-line using National Instruments LabVIEW Programming Software (v7) installed on a Dell Precision Workstation computer. SCR data were DC amplified at a gain of 2000.

Procedure

Parental consent and child assent were obtained prior to the ADIS-C-IV, which was conducted with parent and child approximately 1 week before the first experimental visit. Parents were given questionnaires to be completed and returned at the first experimental visit.

As part of a larger study, children attended three visits, each approx. 2 weeks apart, with conditioning and extinction completed on the second visit and extinction re-test on the third visit. The first visit included a 5 min resting baseline phase (as children watched a silent version of *The Incredibles*) followed by 28 startle habituation trials. The second visit commenced with a 5 min resting baseline phase, followed by 14 startle habituation trials, and the conditioning and extinction paradigms. The third visit included a 5 min resting

baseline phase followed by 14 startle habituation trials, a darkness-induced fear-potentiation protocol, and the extinction re-test. The results of the habituation experiments and the fear-potentiation protocol will be presented in separate reports.

All children were accompanied by one parent to each experimental visit. Each visit began with an adaptation period in which parents and children were familiarized with the laboratory, after which the recording devices were attached.

During conditioning and extinction, children were seated alone, in a sound attenuated room adjacent to the experimental room, interconnected via intercom and closed-circuit cameras from two angles. Parents were situated in a third room, also adjacent to the experimental room. Parents completed diagnostic evaluations and self-report questionnaires as children underwent the experimental procedures. Children were instructed to sit quietly and as still as possible, with their chins in a chin rest.

For the *conditioning phase*, Ps first rated the four geometric shapes using the SAM, and were asked to pay attention to the next series of pictures and loud noises because they would be asked questions about them after the procedure was over. Then, they received 16 trials, 8 CS+ and 8 CS−, presented in random order with the caveat that no more than two trials of either CS were presented sequentially, and that the first two trials were a CS+ and a CS−. The CS+ and CS− were presented either side of a fixation cross, which remained on the screen from CS offset to onset. On CS+ trials, US onset was at 7 s and offset was at 8 s, commensurate with CS+ offset. The CS− was always presented alone. The inter-trial interval (from CS onset to CS onset) varied across 20, 25 and 30 s (mean = 25 s). After the conditioning trials, Ps were asked the contingency awareness questions, re-rated the four geometric figures using the SAM, and were instructed to continue to pay attention for the next phase of the experiment.

The *extinction phase* consisted of 8 trials: 4 CS+ trials without the US pairing and 4 CS− trials. The trials were presented in random order with no more than 2 sequential presentations of either CS. CSs were presented an equal number of times to the left and right of the central fixation cross. Then, the SAM ratings of the four geometric shapes were completed again.

Extinction re-test took place an average of 12 days later (range 5–42 days). Ps first completed the SAM of the four geometric figures, and were then instructed they were to do the same task as they did last time they were in the laboratory when they saw shapes on the screen and heard some sounds. They received 8 extinction re-test trials which were administered in the same manner as during the extinction phase. Finally, Ps repeated their SAM ratings of the four geometric figures.

Response definitions, data screening and statistical analysis

Skin conductance responses—SCR data were inspected for artifacts by trial-by-trial behavioral observations of sneezing, coughing, deep sighs, excessive drowsiness, excessive body movements, and occasions when the child was not looking at the CS+/− when presented on the screen, made via closed-circuit TV, and by additional channels of

recording, including vertical and horizontal EOG (for eye and head movements and gaze shifts) and subclavicular electrodes (for bursts of EMG activity).[2] Trials in which artifacts occurred were rejected. The magnitude of the phasic SCR elicited during each CS was scored within three latency windows as the distance between the trough and apex of the curve, expressed in microsiemens (μS). First interval responses (FIR) were those that began 1–4 s following onset (reflecting initial orienting to the signal value of the CS that is enhanced during CSs paired with a UCS; Ohman, 1983). Second interval responses (SIR), reflecting anticipation of the UCS (Prokasy & Ebel, 1967; Ohman, 1983), began 4–7 s following CS onset. Third interval responses (TIR) began 7–11 s following CS onset (Prokasy & Kumpfer, 1973), and provided a means to compare unconditional responses (URs) across the groups. Separate 3 Group (CON, AR, ANX) × 2 CS (CS+, CS−) × 4 Block (first, second, third, fourth) (average of two trials per block) mixed ANOVAS analyses were conducted on FIR, SIR, and TIR SCR magnitudes.

Of the 12 CON children, SCR data were available from 11 during conditioning (1 discontinued after the first trial), 9 during extinction (2 discontinued after conditioning), and 8 during extinction re-test (1 had unscorable SCR data due to excessive body movements). Of the 16 AR children, SCR data were available from 15 during conditioning (1 withdrew after the first experimental visit), 14 during extinction (1 discontinued after conditioning), and 9 children during extinction retest (2 discontinued after extinction; 3 had unscorable SCR data due to excessive body movements or technical problems). Of the 23 ANX children, SCR data were available from all 23 during conditioning and extinction, and 21 during extinction re-test (2 withdrew after conditioning/extinction).

Verbal ratings—Valence and arousal ratings of the CS+ and CS− were analyzed using a 3 Group (CON, AR, ANX) × 2 CS (CS+, CS−) × 5 Phase (pre-conditioning; post-conditioning; post-extinction; pre-extinction re-test; post-extinction re-test) analysis of variance (ANOVA), on Ps who completed all three phases of conditioning, extinction and extinction re-test. However, 2 ANX Ps did not complete the ratings task correctly, resulting in data from 8 CON, 9 AR, and 19 ANX children available for analysis.

Statistical approach—We followed the statistical approach of Blechert, Michael, Vriends, Margraf, and Wilhelm (2007), who compared acquisition and extinction phases across three groups (adults with PTSD and healthy controls with and without trauma exposure), using SCR and verbal ratings. They conducted separate analyses for each phase, and followed significant Group effects in omnibus analyses with three sets of planned comparisons, between each pair of groups. Thus, we similarly conducted omnibus analyses for each phase, with significant Group effects followed by pair-wise comparisons of ANX vs CON, AR vs CON, and ANX vs AR. All analyses were performed in SPSS version 14.0 (SPSS Inc., Chicago, IL) on square root transformed SCR data (Venables & Christie, 1980), using a linear mixed ANOVAs for repeated measurements with Satterthwaite's Approximation for degrees of freedom. Bonferroni corrections to pair-wise comparisons were applied to control against the accumulation of alpha error. Parameter estimates (i.e., β

[2]Details of the recording for EOG and heart rate are available upon request.

values) are reported as indicators of effect size for significant effects in pair-wise analyses. Exploratory analyses revealed no gender × group interactions, and thus gender was not included in the main analyses.

Results

Symptom measures

Means and standard deviations for the questionnaire measures are displayed in Table 1. Parent MASC total scores differed across groups, $F(2, 42) = 7.81$, $p < .001$, $\eta_p^2 = .27$, with ANX rated higher than CON and AR (both $p < .007$), which did not differ from each other ($p = .98$). Similar results were observed for child MASC total scores, $F(2, 45) = 5.45$, $p = .008$, $\eta_p^2 = .20$, with ANX children's scores higher than CON and AR children (both $p < .03$) which did not differ from each other ($p = .99$). There were no significant differences in CDI *T*-scores across groups, $F(2, 44) = 2.30$, ns.

Control variables

Valence and arousal ratings—Separate 3 Group (CON, AR, ANX) × 4 Stimulus (rectangle, CS+, CS−, circle) ANOVA of valence and arousal ratings prior to the conditioning phase revealed no significant differences, all *F*'s < .93, ns.

First time responding to the CS+ and CS−—A 3 Group (CON, AR, ANX) × 2 CS (CS+, CS−) mixed ANOVA of FIR, SIR, and TIR SCR magnitudes during the first block of conditioning trials (two trials per CS) revealed no significant group effects, all *F*'s < 2.10, ns.

Interval between visits—The number of days between the conditioning-extinction visit and the extinction re-test visit did not differ significantly between groups, $F(2, 35) = .78$, ns.

Contingency awareness—Chi square analyses indicated no significant differences in the number of unaware ANX children ($n = 5$; 22%) or AR children ($n = 5$; 33%) compared with CON children ($n = 2$; 25%) $\chi^2(1) = .02$, ns and $\chi^2(1) = .53$, ns respectively.

Omnibus analyses

SCR—Omnibus analyses yielded significant effects for CS, $F(1, 198) = 3.86$, $p = .05$, and CS × Block interaction, $F(3, 483) = 2.79$, $p = .044$, for FIR during conditioning, indicating discrimination conditioning for the sample as a whole. Also, there were significant main effects of Group for SIR and TIR magnitudes during conditioning, $F(2, 157) = 3.85$, $p = .02$, and $F(2, 121) = 4.23$, $p = .017$, respectively. Extinction data revealed significant main effects of Group for FIR, $F(2, 81) = 4.60$, $p = .01$ and SIR, $F(2, 84) = 3.71$, $p = .03$. Extinction re-test data revealed significant main effects of Group for FIR, $F(2, 61) = 6.16$, $p = .004$, and SIR, $F(2, 69) = 5.06$, $p = .009$. Thus, pair-wise comparisons were conducted on FIR, SIR and TIR for conditioning, and FIR and SIR for extinction and extinction re-test. Contingency awareness did not affect the pattern of results, since the same results were obtained when all omnibus analyses were performed excluding unaware Ps.

Verbal ratings—A 3 Group × 2 CS × 5 Phase mixed ANOVA of valence ratings revealed a significant Group × CS × Phase interaction, $F(8, 62) = 2.50$, $p = .02$, $\eta_p^2 = .24$. There were no significant group effects for arousal ratings, all F's < 1.83, ns. Thus, subsequent pair-wise group comparisons (ANX v CON; AR v CON; ANX v AR) were performed for valence ratings only.

Pair-wise comparisons—For purposes of simplification, only results involving Group as a significant main or interaction effect are described below.[3]

ANX vs CON

Conditioning: Group effects were not significant for FIR, all $F < 2.80$, ns. As shown in Fig. 1, left middle and lower panels, main effects of Group were observed for SIR and TIR, $F(1, 110) = 7.88$, $p < .001$, $\beta = -.15$, and $F(1, 96) = 6.48$, $p = .01$, $\beta = -.12$, respectively. These differences reflected larger anticipatory responses and unconditional responses to the timing of the US collapsed across CS and Block in ANX than CON.

Extinction: Significant Group main effects were found for FIR, $F(1, 58) = 8.12$, $p < .001$, $\beta = -.11$, and SIR, $F(1, 55) = 6.19$, $p = .003$, $\beta = -.10$, reflecting larger orienting and anticipatory responses in ANX than CON, regardless of CS type and Block (see Fig. 1, center upper and middle panels).

Extinction re-test: As depicted in Fig. 1, right upper and middle panels, significant Group main effects were found for FIR, $F(1, 43) = 9.96$, $p < .013$, $\beta = -.18$, and SIR magnitudes, $F(1, 50) = 9.54$, $p = .003$, $\beta = -.09$, reflecting larger orienting and anticipatory responses in ANX than CON that was undifferentiated by CS type or Block and persisted across a 2-week period on average after initial extinction.

Across phases: To test the possibility that the intervening experimental paradigms (i.e., habituation and fear potentiated startle) between the end of extinction and extinction re-test differentially affected the three groups, the last block of extinction and first block of extinction re-test were compared in 2 Group × 2 CS × 2 Phase (last block of extinction, first block of extinction re-test) ANOVAs for FIR, SIR and TIR SCRs. A significant interaction of Group × Phase would potentially indicate differences in the way in which the groups were affected by the intervening paradigms. However, there were only significant Group main effects for FIR, $F(1\ 59) = 7.68$, $p = .008$, $\beta = -.11$, and SIR, $F(1, 62) = 5.48$, $p = .02$, $\beta = -.09$, reflecting larger orienting and anticipatory responses in ANX than CON overall. Group did not interact with CS or Phase, all F's < 1.97, ns.[4] Thus, the intervening habituation and fear-potentiation paradigm did not appear to affect the groups differently.

Valence ratings: ANX and CON children showed different patterns of valence ratings for the CS+ and CS−, Group-CS × Phase $F(4, 22) = 2.75$, $p = .05$, $\eta_p^2 = .33$. Post-conditioning and post-extinction ratings of the CS+ were significantly lower in ANX than CON (both p

[3]A complete set of analyses is available from the authors.
[4]Nor did the Group factor interact with either phase or CS type when evaluating changes from the last trial of extinction to the first trial of extinction re-test.

< .02) (see Fig. 3), whereas the two groups did not differ in their ratings of the CS−. Also, ANX children's ratings of the CS+ were significantly lower than their ratings of the CS− post-conditioning (p = .01), post-extinction (p = .006) and pre-extinction re-test (p = .035), whereas ratings of the CS+ and CS− did not differ within CON children.

AR vs CON

Conditioning: Effects for FIR and SIR were not significant, all F's < 2.60. There was a significant main effect of Group for TIR magnitudes, $F(1, 57) = 7.17$, p = .01, β = −.14, representing larger unconditional responses to the timing of the US, that was undifferentiated by CS type and Block, in AR than CON (see Fig. 2, left lower panel).

Extinction: FIRs yielded a main effect of Group, $F(1, 38) = 4.90$, p = .033, β = −.10, reflecting larger orienting responses regardless of CS type and Block in AR than CON (see Fig. 2, center upper panel). A significant Block × Group interaction, $F(1, 131) = 4.69$, p = .032, β = −.10, was followed with post-hoc tests that indicated that FIRs did not differ between blocks in CON (p = .78) but were significantly larger in the first compared with the second block in AR (p = .002). There were no significant effects for SIR or TIR, all F's < 1.80.

Extinction re-test: Effects for FIR were not significant, all F's < 3.51, whereas there was a significant Group main effect for SIRs $F(1, 29) = 5.03$, p = .033, β = −.09, reflecting larger anticipatory responses collapsed across CS and Block in AR than CON that persisted on average 2 weeks after initial extinction (see Fig. 2, right middle panel).

Across phases: Group main effects were significant in the comparison of TIR from extinction to extinction re-test, $F(1,29) = 6.48$, p = .02, β = −.11, reflecting larger responses in AR than CON overall collapsed across the last block of extinction and the first block of extinction re-test. However, Group effects did not interact with CS or Phase, all F's < .2.08, ns.

Valence ratings: There were no significant Group effects, all F's < 2.47.

ANX vs AR

Conditioning: There were no significant effects for FIR or TIRs, all F's < 2.15, whereas there was a main effect of Group in the analysis of SIRs, $F(1, 118) = 4.00$, p = .05, β = −.11, reflecting larger anticipatory responses in ANX than AR.

Extinction and extinction re-test: There were no significant effects involving Group, all F's < 2.25 and 1.31, respectively.

Across phases: Group effects were not significant, all F's < 1.83, ns.

Valence ratings: The Group × CS × Phase interaction was significant, $F(4, 23) = 3.30$, p = .03, η_p^2 = .31, due to lower ratings of the CS− prior to extinction re-test in AR than ANX (p = .002).

Discussion

The goal of this study was to evaluate discrimination conditioning and extinction as markers of risk for anxiety disorders in children. The findings indicated that the sample as a whole exhibited discriminative conditioning to CS+ vs CS− trials in orienting responses (i.e., FIR magnitudes). This effect was not moderated by group but there were other group differences. During conditioning, anxiety disordered children exhibited stronger anticipatory responding (i.e., SIR magnitudes) and stronger responding to the timing of the US (i.e., TIR magnitudes), to both CS+ and CS− trials, relative to controls. Their stronger anticipatory responding was sustained throughout extinction and extinction re-test, again to both CS+ and CS−, relative to controls. Furthermore, the anxiety disordered group showed larger orienting responses (i.e., FIR magnitudes) to both CS+ and CS− by extinction and extinction re-test in comparison to controls.

During conditioning, at-risk children differed from controls only in their responding to the timing of US (i.e., TIR magnitudes), again to both CS+ and CS− trials. However, at-risk children showed further differences from controls over the course of extinction and extinction re-test. That is, relative to controls, at-risk children showed an initially stronger orienting response (i.e., FIR magnitudes) at the start of extinction, undifferentiated by CS type that subsided as extinction trials continued. By extinction re-test, they showed significantly larger anticipatory responding (i.e., SIR magnitudes), again undifferentiated by CS type, that did not subside over trials. Moreover, the ‘enhancement’ of responding in at-risk children by extinction re-test resulted in them no longer differing from anxiety disordered children, at least in terms of anticipatory responding, despite significantly lower anticipatory responding than anxiety disordered children during conditioning.

Thus, relative to controls, the stronger anticipatory responding that was consistently observed in conditioning, extinction and extinction re-test in anxiety disordered children appeared to ‘incubate’ in at-risk children and manifest by extinction re-test. One interpretation of these findings is that initially high levels of anticipatory anxiety in the context of an aversive event are characteristic of the manifestation of anxiety disorders whereas a delayed upsurge in anticipatory anxiety is characteristic of familial risk status. Stronger orienting responses throughout extinction and extinction re-test were additionally characteristic of anxiety disorders, but only weakly characteristic of risk status, relative to controls. Thus, of these two, anticipatory responses appear to be more shared between anxiety disordered and at-risk children.

In addition to skin conductance arousal responses, we measured verbal ratings of arousal and valence for the CS+ and CS− to obtain an index of affective learning (Lipp, 2006). The fact that the groups did not differ in their verbal arousal ratings indicates discordance between verbal and physiological indices of arousal, since larger arousal responses (i.e., skin conductance) were observed to both the CS+ and CS− in anxiety disordered and, to a lesser degree, at-risk children. Discordance between physiological and subjective measures has been long recognized (e.g., Lang, 1971). Also, anxiety disordered children rated the CS+ as less pleasant at post-conditioning and post-extinction than control children, while they did not differ from controls in their ratings of the CS−. They also rated the CS+ as less pleasant

than the CS− at post-conditioning, post-extinction, and pre-extinction re-test, whereas controls did not rate the two stimuli differently. Thus, it appears that anxiety disordered children learned to judge the CS+ more negatively than the CS−, in away that was resistant to extinction and persisted until extinction re-test, whereas control children remained indiscriminate in their labeling of these stimuli. These findings share some similarities with the report by Liberman et al. (2006), in which anxious children did not vary their arousal ratings, but did rate the CS+ as more unpleasant after extinction than acquisition; the reverse pattern of pleasantness ratings occurred in control children. Conceivably, valence ratings are a more sensitive measure of affective learning and it's resistance to extinction than arousal ratings, at least in anxious children.

At-risk children did not differ from control children in terms of valence ratings. Thus, anxiety disordered and at-risk children both differed from controls in terms of anticipatory skin conductance responding, whereas anxiety disordered children *additionally* differed from controls in verbally reported valence. Elevated negative valence judgments, therefore, may be a response specific to the manifestation of anxiety disorders and not shared with familial risk for anxiety disorders. Unfortunately, we did not collect physiological indices (i.e., startle reflexes) of emotional valence, something we plan to do in future research.

The three groups of children appeared to enter the laboratory environment at similar levels of emotional state and arousal. That is, there were no group differences in initial ratings of the valence or arousal for the four geometric figures, including the CS+ and CS−. There also were no group differences in skin conductance responding to the first two trials of conditioning. Furthermore, the three groups appeared to learn the contingencies of the aversive conditioning to the same degree. Approximately 22–33% of each group did not correctly identify the connection between the CS+ and the aversive tone, a rate that is slightly lower than the rate typically reported in adult samples (e.g., Chan & Lovibond, 1996; Dawson & Reardon, 1973); there is no reference for comparison in children. Thus, neither baseline effects nor contingency awareness appear to explain the group differences in arousal and valence ratings throughout the experiment. Furthermore, the effects do not appear to be due to depression, given the lack of group differences on the depression measure.

Elevated responding to both CS+ and CS− has been attributed to associative processes of elevated excitatory responding to threat cues (CS+) and poor inhibitory responding to safety cues (CS−), and overgeneralization, as well as non-associative processes of sensitization and habituation (see Lissek et al., 2005, for a review). Associative processes are especially viable when responding is stronger to the CS+ than the CS−, but when responding is indiscriminately elevated to both CS+ and CS−, as was the case in our group comparisons, non-associative processes become equally viable. Indeed, the larger third interval skin conductance responses during timing of delivery of the US (and its omission), collapsed across all conditioning trials, in anxiety disordered and at-risk children suggests that they were more aroused by the loud tone than controls; this is relevant because arousal heightens sensitization (Groves & Thompson, 1970). On the other hand, the groups did not differ on the first two trials to either the UCS or the novel stimuli of the CS+ and CS−, when effects of arousal and sensitization would be most apparent. Moreover, sensitization is a transient

process (Groves & Thompson, 1970) and therefore unlikely to explain the group differences at extinction re-test, on average 2 weeks later. Another non-associative explanation is that habituation across the experimental phases was delayed in anxiety disordered and at-risk children compared to control children. However, the lack of dishabituation (i.e., increased strength of responding to stimuli that typically occurs following an intervening interval of time) within control children from the end of extinction to the beginning of extinction re-test argues against habituation as a primary mechanism for the current set of findings.

Therefore, the results may be interpreted as stronger excitatory responses to a cue that signaled threat (CS+) and more difficulty inhibiting arousal responses to a cue that was understood (from contingency awareness ratings) to signal safety (CS−) in anxiety disordered and at-risk children compared to controls. As such, these associative processes may have led anxiety disordered and at-risk children to exhibit elevated undifferentiated responding to both stimulus cues during conditioning, that persisted during extinction (less robustly in at-risk children) when new learning should have occurred about the CS−noUCS association, and extended until approximately 2 weeks later during extinction re-test. The explanatory role of overgeneralization (i.e., lack of discrimination between the stimulus features of the CS+ and CS− stimuli) is rendered less viable by the contingency awareness data that indicated clear stimulus distinction for the majority of participants. However, the role of associative vs non-associative mechanisms remains open to further investigation.

There were several study limitations, including the relatively small sample size, especially for control Ps, and the need for replication. Given the high prevalence of anxiety disorders (e.g., Kessler, Berglund, Demler, Jin, &Walters, 2005), it is not surprising that recruitment of non-anxious children of parents with no history of current or past anxiety disorders was problematic, especially when combined with a burdensome requirement of attendance at the psychophysiological laboratory on multiple occasions. It was also for this reason that it was not possible to evaluate sex differences, which could potentially be quite significant (see Liberman et al., 2006). For the same reason, we were unable to evaluate differences between children with different types of anxiety disorders.

Second, reliance on a relatively mild UCS and a limited number of conditioning trials may have limited the strength of observed group differences. Third, the geometric figures used for CS+ and CS− were not counterbalanced. However, their neutrality and equality in stimulus properties (e.g., luminance) most likely mitigated differential effects of conditioning specific to one geometric figure vs the other.

Fourth, even though the groups did not differ in contingency awareness, our measure was limited to post-conditioning ratings, which represent a reflection and judgment of the totality of the experience once the threat of aversive stimuli is removed. On-line expectancy ratings may yield different results, since strength of skin conductance responding throughout conditioning may be guided by ongoing expectancies for the US (Lipp & Purkis, 2006) and such expectancies may be particularly elevated in anxious individuals (Chan & Lovibond, 1996). Thus, ongoing uncertainty about whether the aversive tone was linked only to the CS + during conditioning may partially explain the group differences.

Fifth, despite our efforts, we were unsuccessful in administering the full diagnostic interview to both parents, and on occasion relied on the attendant parent to report on the parent who was not available for interview. This was most critical for the control group, for whom we were successful in interviewing all mothers but only 6 (out of 11) fathers. Although the mothers reported that the fathers had never reported nor been treated for anxiety or mood disorders, we cannot be sure that this was the case. Related to this issue is that our at-risk group was comprised of a heterogeneous group of parental anxiety disorders, some with major depression as well. Different results may have occurred with a more homogenous parent group. It is also possible that the inclusion of additional risk variables, such as childhood temperament, may have yielded further differences between our at-risk and control children. In other words, temperaments such as neuroticism, that predict later anxiety disorders (e.g., Hayward et al., 1998), may either mediate and/or contribute additive effects to the effects of familial risk status upon aversive conditioning. Future research might evaluate the degree to which characteristics of aversive learning in clinically anxious youths, as well as those at-risk for anxiety through familial status, are explained by individual difference variables.

In conclusion, albeit in need of replication, the current results indicate that anxiety disordered and at-risk children differed from control children in patterns of responding during aversive conditioning and extinction. The elevated conditioned skin conductance responding, present from the conditioning phase in anxiety disordered children, and emergent by extinction in at-risk children, to both CS+ and CS− trials, suggests that elevated excitatory responding to threat cues and impaired inhibition of responses to safety cues may be processes that underlie the expression of childhood anxiety disorders and contribute to their development. Negative valence judgments for stimuli paired with aversive stimuli, characteristic of anxiety disordered children, may additionally contribute to excessive anxiety. In our future studies, we will use startle eye blink responses to probe the neurophysiological component underlying the negative valence reports.

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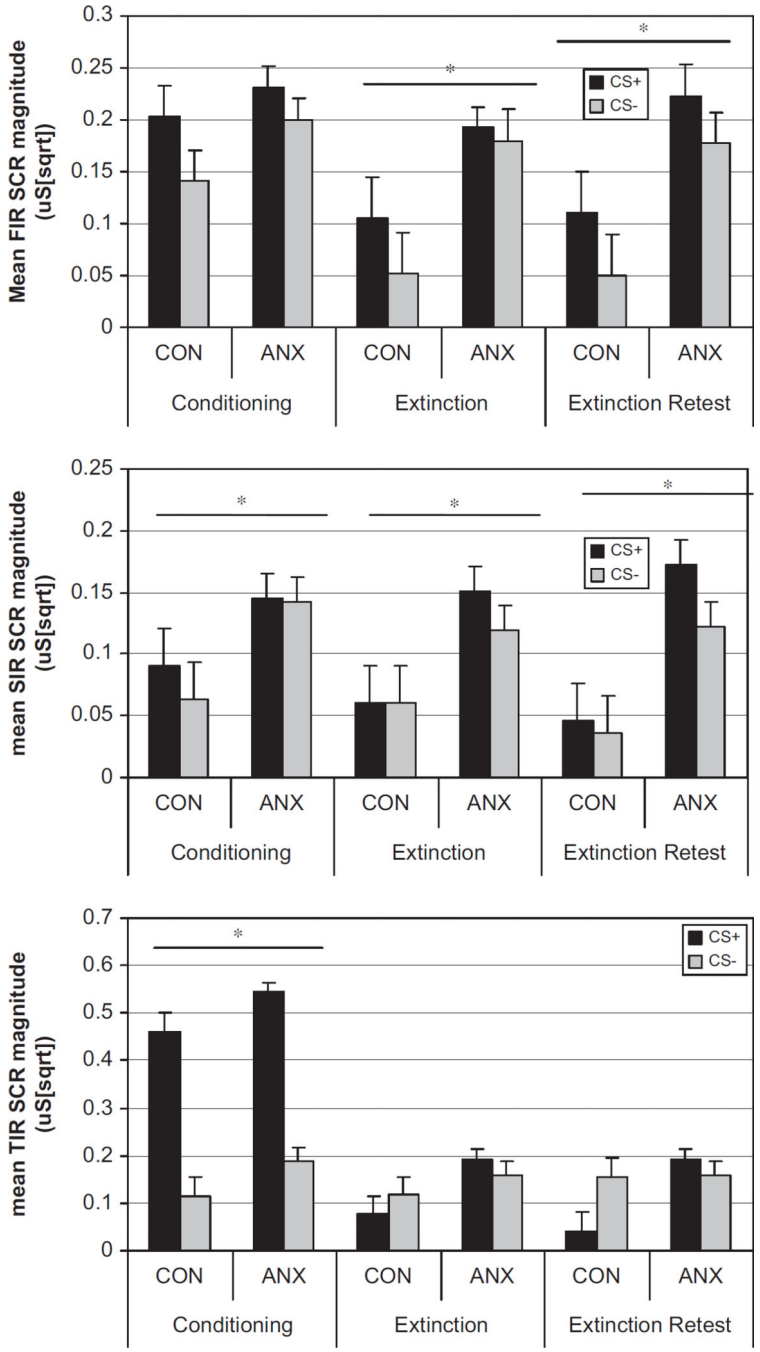

Fig. 1.

Mean SCR magnitudes to the CS+ and CS− for first interval (upper panel), second interval (middle panel), and third interval responses (lower panel) during conditioning (left panel), extinction (center panel), and extinction re-test (right panel) for anxious and control children. All analyses showing significant Group main effects are displayed with *.

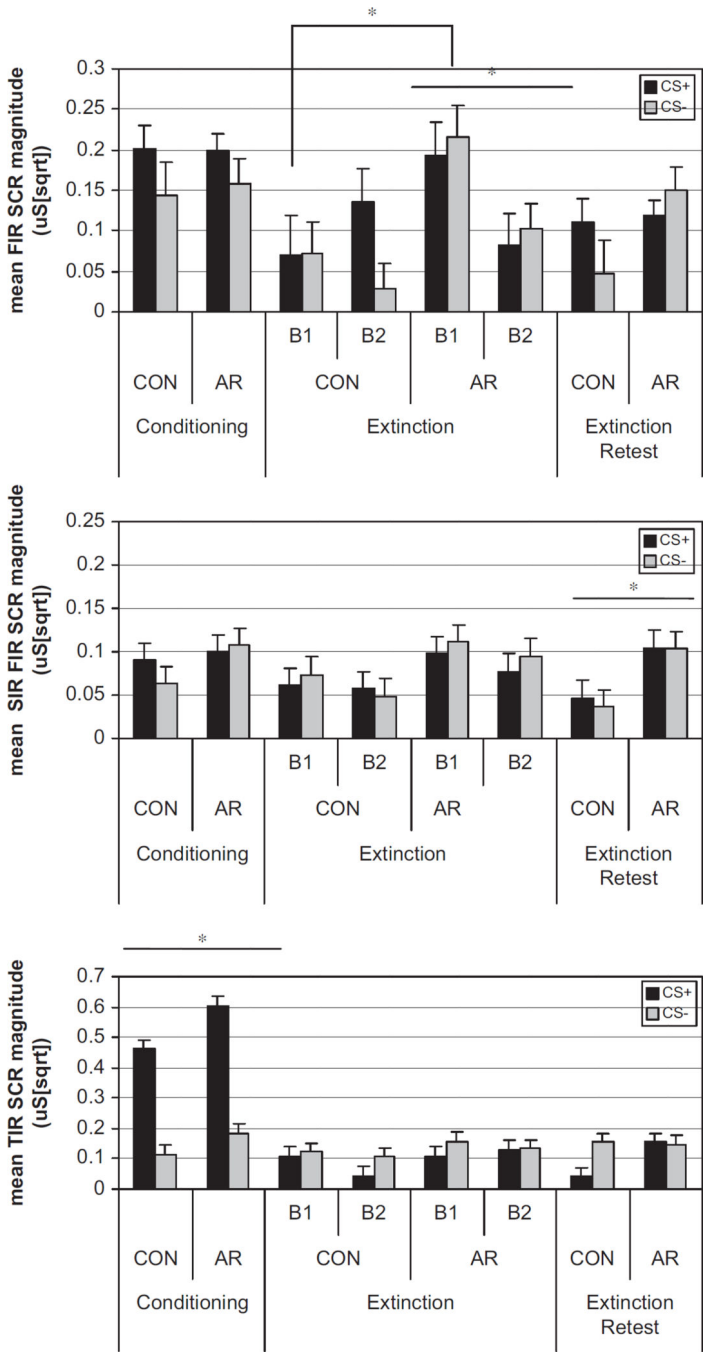

Fig. 2.

Mean SCR magnitudes to the CS+ and CS− for first interval (upper panel), second interval (middle panel), and third interval responses (lower panel) during conditioning (left panel), extinction (centre panel), and extinction-retest (right panel) for at-risk and control children. All analyses showing significant Group main effects are displayed with *.

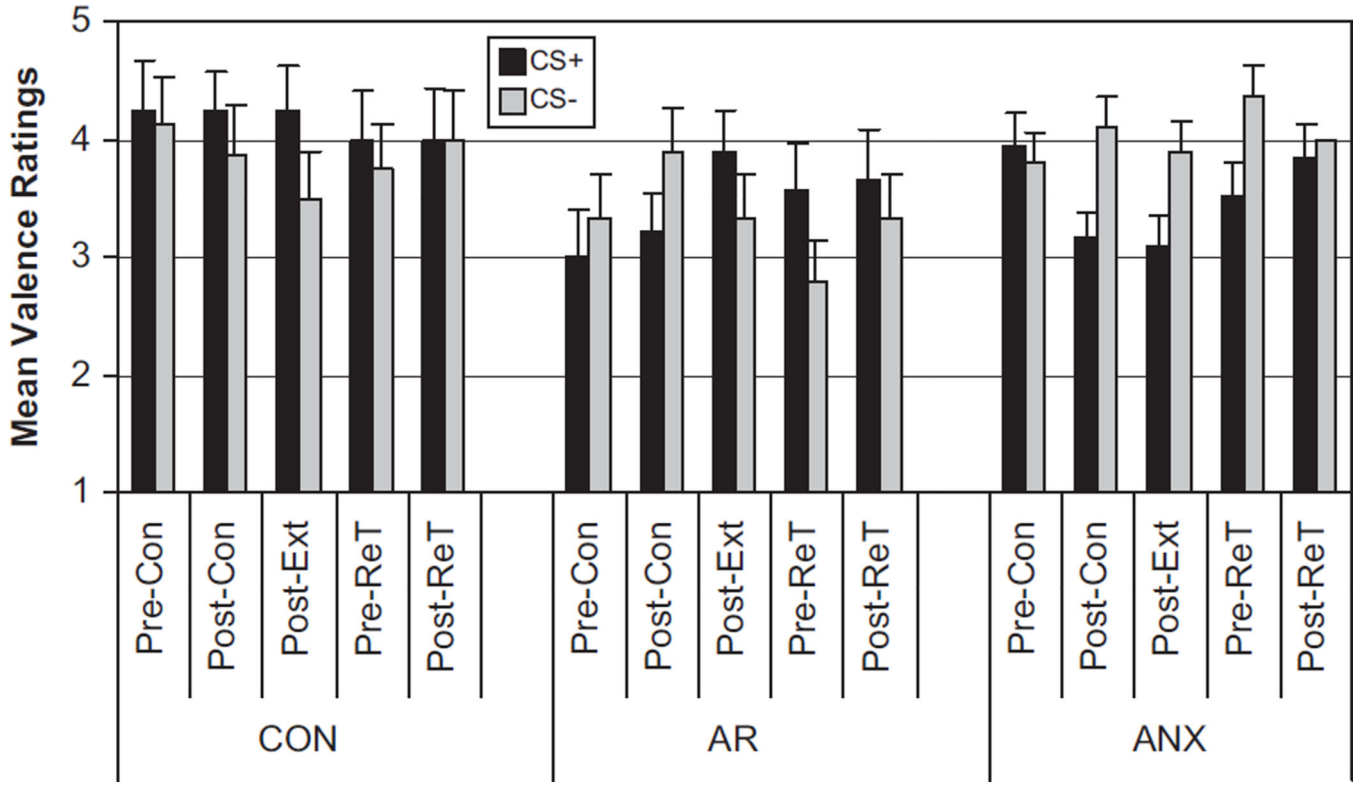

Fig. 3.

Mean valence ratings (+SE) of the CS+ and CS− at pre- and post-conditioning, post-extinction, and pre- and post-extinction retest as a function of group.

Table 1

Means and standard deviations for each questionnaire measure as a function of group

Measure	Anxious Mean (SD)	At-risk Mean (SD)	Control Mean (SD)
Parent report			
MASC-P[a]	55.15 (7.21)	45.00 (10.76)	44.55 (8.43)
Child report			
MASC-C[b]	55.39 (9.13)	46.64 (9.38)	46.36 (9.55)
CDI[c]	45.82 (9.99)	41.00 (4.91)	40.64 (6.04)

Note MASC-P = Multidimensional Anxiety Scale for Children, Parent Report; MASC-C = Multidimensional Anxiety Scale for Children, Child Report; CDI = Children's Depression Inventory *T*-scores.

[a] Based on data from $N = 20$ ANX, $N = 14$ AR, and $N = 11$ CON children.

[b] Based on data from $N = 23$ ANX, $N = 14$ AR, and $N = 11$ CON children.

[c] Based on data from $N = 22$ ANX, $N = 14$ AR, and $N = 11$ CON children.