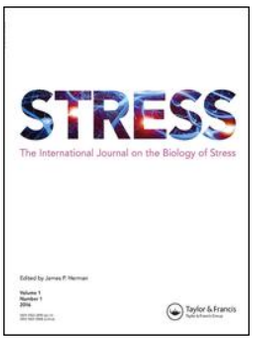

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ORIGINAL RESEARCH REPORT

Uncontrollable and unpredictable stress interacts with subclinical depression and anxiety scores in determining anxiety response

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Abstract

According to learned helplessness theory, uncontrollable stress is assumed to be a critical etiological factor in the pathogenesis of depression. In contrast, unpredictability of stressors is assumed to facilitate the development of sustained anxiety. Despite the frequent co-morbidity of depression and anxiety disorders, these two factors have rarely been studied simultaneously in humans. Therefore, we investigated whether there are interaction effects of uncontrollability and unpredictability on anxiety response in healthy participants. Seventy-nine healthy participants performed a visual dot probe task with emotional faces, while receiving mild electrical shocks in four different conditions (2×2 factorial design). In (un)controllable conditions, participants were (not) able to attenuate shock intensity. In (un)predictable conditions, participants were (not) able to anticipate shock occurrence. Before the experiment, participants' subclinical depression and anxiety scores were measured using the Beck Depression and Anxiety Inventories (BDI/BAI). During the experiment, continuous skin conductance and self-reported state anxiety were assessed and attentional biases towards angry faces were calculated. As expected, participants showed greater anxiety in uncontrollable compared to controllable and in unpredictable compared to predictable conditions. Additionally, anxiety decreased within the test sessions in participants with low BDI/BAI scores but not in participants with higher BDI/BAI scores. Most importantly, controllability and predictability interacted with each other and with BDI/BAI scores with regard to anxiety. Our results provide evidence that uncontrollability and unpredictability of stressors not only have separate but also interaction effects on several anxiety measures in susceptible individuals and may provide insights into the psychological mechanisms underlying a depressive/anxiety co-morbidity.

Keywords

Behavioral control, prediction, stress response, electrodermal activity, affective disorders, anxiety learning

History

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Introduction

Depression and anxiety disorders are among the most common and costly diseases in the world (Beddington et al., 2008; Greenberg et al., 2003; Kessler et al., 2005). They occur co-morbidly strikingly often with more than 50% of depressed patients reporting a lifetime history of anxiety disorders (Kaufman & Charney, 2000; Kessler et al., 2005). The presence of a co-morbid pathology substantially increases life impairment of patients and is associated with worse treatment outcome and increased likelihood of chronicity (Hirschfeld, 2001). However, there is still limited understanding of the psychological mechanisms underlying these disorders and their frequent co-morbidity.

Stress is the main known etiological factor associated with the pathogenesis of affective disorders (Kendler et al., 1999). However, the nature of the stress experience determines its impact on psychological health. For example, behavioral or cognitive control over stressors (referred to as *controllability*) and predictability of stressors have been suggested to moderate the stress experience and its negative influences on health (Hammen, 2005). The effects of controllability and predictability have initially been investigated simultaneously in animals (Mineka & Kihlstrom, 1978; Seligman, 1975; Thomas & Dewald, 1977; Wolpe, 1958). However, in accordance with the suggestion that experiencing uncontrollability generally leads to depression, whereas experiencing unpredictability generally leads to anxiety (Seligman, 1975), subsequent research mainly investigated either the individual

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effects of uncontrollability or the individual effects of unpredictability separately (Zvolensky et al., 2000).

Encouraged by the popularity of the *Learned Helplessness Model* (Maier & Seligman, 1976), many researchers focused on the impact of uncontrollable stress in the development of depression (see e.g., Pryce et al., 2011 for a review of animal and human evidence). Maier and Seligman (1976) demonstrated that animals confronted with uncontrollable stress developed escaping deficits whereas those confronted with the same amount of controllable stress did not. Experiments in healthy humans replicated these findings by demonstrating feelings of helplessness, behavioral changes (error rates and reaction times) and slow cortical potential changes during and after exposure to uncontrollable compared to controllable stress (Diener et al., 2009). Additionally and importantly, this influence of uncontrollability was more pronounced in depressed patients compared to healthy controls (Diener et al., 2009). Furthermore, other studies demonstrated that the perception of controllability not only prevents immediate negative effects of stress and immunizes against future situations of uncontrollable stress (Diener et al., 2009), but also reduces anxiety regarding future aversive events (such as pain stimuli, see e.g. Salomons et al., 2004; Wiech et al., 2006).

Concerning predictability, Grillon and others have investigated the effects of unpredictable stressors on sustained contextual anxiety. They showed in several experiments that unpredictable aversive events increased sustained anxiety, whereas predictable events only increased phasic cued fear of the specific signaling cue (Grillon et al., 2004; Mol et al., 2007). They posited the *Safety Signal Hypothesis* (Grillon, 2002) as a potential explanation for this finding: if an aversive event is signaled by a cue, the absence of that cue signals the absence of danger or the presence of safety. However, if the aversive event is not signaled by a cue and is thus unpredictable, there are no periods of safety and the individual remains in a state of sustained anxious anticipation. Furthermore, they demonstrated that anxiety of unpredictable but not predictable aversive events was increased in high anxious individuals and in patients with panic disorders and post-traumatic stress disorder (Glotzbach-Schoon et al., 2013; Grillon et al., 2008, 2009).

Experiments in rats have provided strong evidence that the stress buffering effects of controllability and predictability are mediated by two different neural pathways (Christianson et al., 2008). It is assumed that when stressors are controllable, the stress-induced activation of the dorsal raphe nucleus is inhibited by the ventromedial prefrontal cortex (Amat et al., 2005). On the other hand, the anxiety-preventing effects of predictability seem to be mediated by the posterior insula, which in turn inhibits the amygdala (Christianson et al., 2008). These neural underpinnings indicate that uncontrollability and unpredictability may not only have separate effects but also have the neurobiological potential for interaction effects via connection between the amygdala and the dorsal raphe nucleus (Peyron et al., 1998). Considering the susceptibility of depressed patients to uncontrollability (Diener et al., 2009) and the susceptibility of anxiety patients to unpredictability (Grillon et al., 2008, 2009), we hypothesized that the co-occurrence of experimental stressors that are both uncontrollable and unpredictable would act additively or even synergistically on anxiety response in participants.

Despite the considerable scientific interest in the concepts of controllability and predictability, only a few studies have examined them simultaneously in humans. On the contrary, most studies did not differentiate between them or even confounded them (Miller, 1979; Zvolensky et al., 2000). One study that did investigate both factors simultaneously in a sample of healthy participants found separate effects on heart rate reactivity but no interaction effects (Baker & Stephenson, 2000). Because of this, we hypothesized that interaction effects may be restricted to participants with subclinical symptoms of depression or anxiety disorders. Thus, we developed a paradigm to simultaneously examine the effects of the uncontrollability and unpredictability of a stressor (i.e. mild electrical shocks) on multiple anxiety measures (skin conductance, self-reported anxiety and attentional bias towards threat) and the Positive and Negative Affect Schedule (PANAS) as a state measure of mood (Watson et al., 1988) in a sample of healthy participants. Notably, our sample showed varying levels of subclinical depression and anxiety scores as assessed by the Beck Depression Inventory (BDI; Beck et al., 1961) and the Beck Anxiety Inventory (BAI; Beck et al., 1988). We tested the following three hypotheses: (1) separate main effects of stressor uncontrollability and unpredictability can be found on the anxiety measures, (2) participants with elevated depression scores are particularly susceptible to uncontrollability, whereas participants with more pronounced anxiety scores are particularly susceptible to unpredictability, and (3) under inclusion of the depression and anxiety scores of the participants, interaction effects of uncontrollability and unpredictability will be found.

Methods

Participants

Seventy-nine participants (42 males and 37 females; aged 18–37 years, 24.15 ± 4.75 [*SD*]) took part in the experiment. They were recruited via online advertisements on the University of Zurich website. All participants reported no past or present neurological or psychiatric diseases requiring treatment and no sensory impairments or subjective cognitive impairments. Additional exclusion criteria were regular illegal drug use, regular use of prescription drugs and left-handedness. All participants were instructed to abstain from drinking alcohol for 24 h before the experiment. The presented study was approved by the Ethics Committee of the Canton Zurich. All participants gave written informed consent prior to the study and received a moderate financial compensation for participation.

Task

Individuals had to perform a visual dot probe task (Bradley et al., 1999; Koster et al., 2004; Mogg et al., 1997), while being under threat of receiving multiple mild electrical shocks. On a computer screen (placed 50 cm in front of them), a fixation cross (1000 ms), two faces (50 ms), and a dot appearing in the former place of one of the two faces (1000 ms), were presented consecutively. Intertrial intervals

varied randomly between 750 ms and 1000 ms (as described previously: Herry et al., 2007). Participants were informed that they had to respond to the position of the dot by pressing a keyboard button (right or left). Face pictures depicted either pairs of two neutral faces or pairs of a neutral and an angry face, which were chosen from the Ekmann set (Ekman & Friesen, 1975) and were previously selected and morphed to optimize affect recognition performance in a normative sample (Schmidt-Daffy, 2011). Using a within-subject design, the participants had to perform all four experimental conditions (see below) whereby each condition consisted of 80 trials (40 neutral-neutral pairings, 40 neutral-angry pairings, see below) and an approximate length of 3 min (depending on the average reaction time of each individual).

Stressor controllability and predictability

During each of the four conditions, each participant received exactly eight mild electrical shocks (300 V, 1000 ms, either 19 or 26 mA, see below) applied to the back of their right hand via foam electrodes with conductive adhesive hydrogel using a commercially available electric stimulation device (Constant Current Stimulator, model DS7A; Digitimer, Hertfordshire, UK). A 2×2 factorial design was used to implement stressor controllability and predictability during the four conditions of the visual dot probe task: *controllable-predictable* (C + P+), *controllable-unpredictable* (C + P−), *uncontrollable-predictable* (C − P+) and *uncontrollable-unpredictable* (C − P−). Individuals were informed that under controllable conditions (C + P+, C + P), shocks were attenuated if they responded fast enough to the position of the dot, whereas in uncontrollable conditions their response speed would have no effect on shock intensity. In fact, based on previous pilot studies, shock intensity was presented in both conditions (19 mA in controllable and 26 mA in uncontrollable conditions) independent of subject's response speed, to ensure the experience of control in all participants. Furthermore, participants were told that in predictable conditions (C + P+, C − P+), shocks would only occur after a danger cue and never after a safety cue, whereas in unpredictable conditions, shocks would occur independently of cue. The danger and safety cues were implemented using two different shapes of the fixation cross. Specifically, the fixation cross was either presented as a straight (''+'') or oblique (''x'') cross. Hereby, in predictable conditions, the respective cue signaling danger appeared in 20 trials, whereas the cue signaling safety appeared in 60 trials. Individuals were informed before each condition, which cue signaled danger. In unpredictable conditions, the occurrence probability (20 trials vs. 60 trials) of the two forms (''+'' vs. ''x'') was similar; however, they were unrelated to shock occurrence. Cues were counterbalanced across participants and semi-randomized across conditions. The order of the four conditions was counter-balanced across participants.

Anxiety measures

Skin conductance

Continuous skin conductance (SC) was recorded during task performance as a measure of physiological arousal using the BioPac System and MP30 Acquisition Box (BIOPAC Systems Inc., Goleta, CA) with the corresponding isotonic gel electrodes (11 mm contact area) placed on the palmar surfaces of the distal phalanx of the first and second digits of the left hand (Scerbo et al., 1992). Data pre-processing and analysis were performed with the MATLAB toolbox *SCRalyze* (http://scralyze.sourceforge.net) using a convolution model for how sudomotor bursting causes fluctuations in skin conductivity. This approach has been shown to be a better predictor of autonomic arousal than conventional measures (Bach et al., 2010).

Self-reported anxiety

Self-reported anxiety was assessed as a measure of subjective anxiety twice during each experimental condition (once after approximately 20 trials and once after approximately 60 trials) on a visual analog scale ranging from 1 to 10 (1 = ''I am not feeling anxious/nervous at all'', 10 = ''I am feeling extremely anxious/nervous'').

Attentional bias

Attentional bias towards angry faces was used as a measure of selective attention towards threat (Bradley et al., 1999; Koster et al., 2004; Mogg et al., 1997). To calculate the attentional bias, trials with neutral-angry pairings were divided into *congruent trials* (in which the dot appeared in the former position of the angry face) and *incongruent trials* (in which the dot appeared in the former position of the neutral face). Then, mean reaction times in congruent trials were subtracted from mean reaction times in incongruent trials for each individual. It must be noted that we focused on attentional biases from non-danger trials for further analyses to solely compare effects of sustained anxiety without confounds of phasic cued fear from the predictable conditions.

Procedure

Individuals were introduced to the experiment and were asked to fill out the BDI (Beck et al., 1961) and the BAI (Beck et al., 1988). Then, SC and electrical stimulation electrodes were attached and participants were presented with written instructions for the visual dot probe task on the computer screen followed by a first practice trial. During the experiment, they were explicitly informed before each condition which condition would follow and had to go through a short practice trial tailored for this specific condition. After every condition, we additionally assessed a state measure of participants' mood using the PANAS (Watson et al., 1988). However, we did not find any significant results and because of this the PANAS data are not presented here. Following completion of the experiment, participants were debriefed and asked about whether they have experienced control over stressors in the controllable conditions.

Statistical analyses

Effects of stressor controllability and predictability were analyzed separately for each anxiety measure using analyses of variance (ANOVA) with the factors: *controllability* (controllable vs. uncontrollable) and *predictability* (predictable vs.

unpredictable). Influences of BDI and BAI scores were subsequently analyzed using analyses of covariance (ANCOVA) with continuous *BDI* and *BAI scores as* covariates. To illustrate the hereby discovered interactions, we used a $2 \times 2 \times 2 \times 2$ ANOVA with the factors *controllability*, *predictability*, *BDI* (low vs. high BDI scores, using the median split = 4), and *BAI* (low vs. high BAI scores, using the median split = 8). For self-reported anxiety, we additionally included the factor *time* (anxiety assessed after 20 trials vs. after 60 trials during each condition) into our analyses. Finally, *post hoc t*-tests corrected for multiple comparisons (Bonferroni) were conducted on the basis of significant ANOVA effects. Statistical analyses were conducted with SPSS (Version 20.0, Chicago, IL) and results were considered significant if $p < 0.05$ after correction for multiple comparisons.

Results

Manipulation check and group stratification

In the manipulation check of controllability after the experiment, 97.5% of all participants reported to have experienced behavioral control (of attenuating the shocks themselves). As a manipulation check of predictability, reaction times (RT) were shorter in trials following danger cues compared to trials following no-danger cues in predictable but not in unpredictable conditions. This indicates increased response speed of participants when anticipating shocks (Table S1).

BDI and BAI scores were significantly correlated ($r(79) = -0.33$, $p = 0.003$). BDI scores ranged from 0 to 30 (4.9 ± 4.96 [*SD*]) and BAI scores from 0 to 39 (11.38 ± 10.34). Within both stratified groups (low vs. high BDI and low vs. high BAI scores), participants did not differ regarding age, sex distribution or education (Table 1). They also did not differ regarding average RT or average anxiety scores in all three measures (SC, self-reported anxiety, attentional bias) except for a difference in SC between participants with low and high BDI scores (Table 1).

Separate effects of controllability and predictability

Investigating the influence of stressor controllability and predictability on anxiety, we found significant main effects for both *controllability* ($F(1,78) = 10.38$, $p < 0.01$) and *predictability* ($F(1,78) = 6.00$, $p < 0.05$) in SC, a significant effect for *controllability* in self-reported anxiety ($F(1,78) = 23.14$, $p < 0.001$) and an almost significant effect for *predictability* in attentional bias ($F(1,78) = 3.77$, $p = 0.056$). However, there was no significant interaction effect of *controllability by predictability* in any measure. The main effects of *controllability* and *predictability* indicated higher SCs (Figure 1A) and higher self-reported anxiety (Figure 1B) in conditions with uncontrollable shocks (compared to conditions with controllable shocks) and higher SCs (Figure 1A) and higher attentional biases (Figure 1C) in conditions with unpredictable shocks (compared to conditions with predictable shocks). Furthermore, comparing SC in the four individual conditions revealed that C − P− elicited highest SC, followed by C − P+, which in turn was followed by C + P − and lowest SC was elicited in C + P + (Figure 1A).

Interactions of controllability and predictability with subclinical scores

Introducing BDI and BAI scores as continuous covariates in our calculations revealed significant interaction effects in SC and self-reported anxiety. Beyond the remaining significant main effects of *controllability* and *predictability* in all measures, we observed interactions of *predictability by BAI scores* in SC ($F(1,76) = 4.07$, $p < 0.05$) and of *controllability by BDI scores by time* ($F(1,76) = 5.63$, $p < 0.05$) and *predictability by BAI scores by time* ($F(1,76) = 4.87$, $p < 0.05$) in self-reported anxiety. To illustrate the discovered interactions, we then stratified participants into groups with low vs. high BDI scores and with low vs. high BAI scores. As above, we found significant main effects of *controllability* and *predictability* in SC, a significant main effect of *controllability* in self-reported anxiety and a significant main effect for *predictability* in attentional bias (Table 2). Additionally, we

Table 1. Demographic data and average anxiety scores for participants with low vs. high BDI and BAI scores (means and SD/frequency data).

	Low BDI ($n = 45$) mean (*SD*)/*N*	High BDI ($n = 34$) mean (*SD*)/*N*	*t (df)*/X^2*(df)*	*p*
Age	24.0 (4.9)	24.3 (4.6)	−0.3 (77)	0.792
Sex (male/female)	26/19	16/18	0.9 (1)	0.371
Education (secondary/higher)	7/38	3/31	0.8 (1)	0.502
Average reaction time (ms)	360.0 (54.0)	355.8 (32.1)	0.4 (77)	0.692
Average skin conductance (μmho)	0.9 (0.6)	0.6 (0.5)	2.5 (77)	0.013
Average self-reported anxiety (points)	4.2 (1.8)	3.9 (1.3)	1.0 (77)	0.339
Average attentional bias (ms)	−1.6 (9.4)	0.1 (11.2)	−0.8 (77)	0.448
	Low BAI ($n = 37$) mean (*SD*)/*N*	High BAI ($n = 42$) mean (*SD*)/*N*	*t (df)*/X^2*(df)*	*p*
Age	24.6 (5.2)	23.8 (4.3)	0.8 (77)	0.440
Sex (male/female)	20/17	22/20	0.0 (1)	0.999
Education (secondary/higher)	5/32	5/37	0.0 (1)	0.999
Average reaction time (ms)	366.3 (56.1)	351.0 (33.2)	1.5 (77)	0.139
Average skin conductance (μmho)	0.7 (0.5)	0.9 (0.6)	−1.2 (77)	0.241
Average self-reported anxiety (points)	3.8 (1.6)	4.3 (1.7)	−1.6 (77)	0.115
Average attentional bias (ms)	−1.4 (10.0)	−0.4 (10.4)	−4.3 (77)	0.671

BAI = Beck Anxiety Inventory (BAI) median split, BDI = Beck Depression Inventory (BDI) median split.

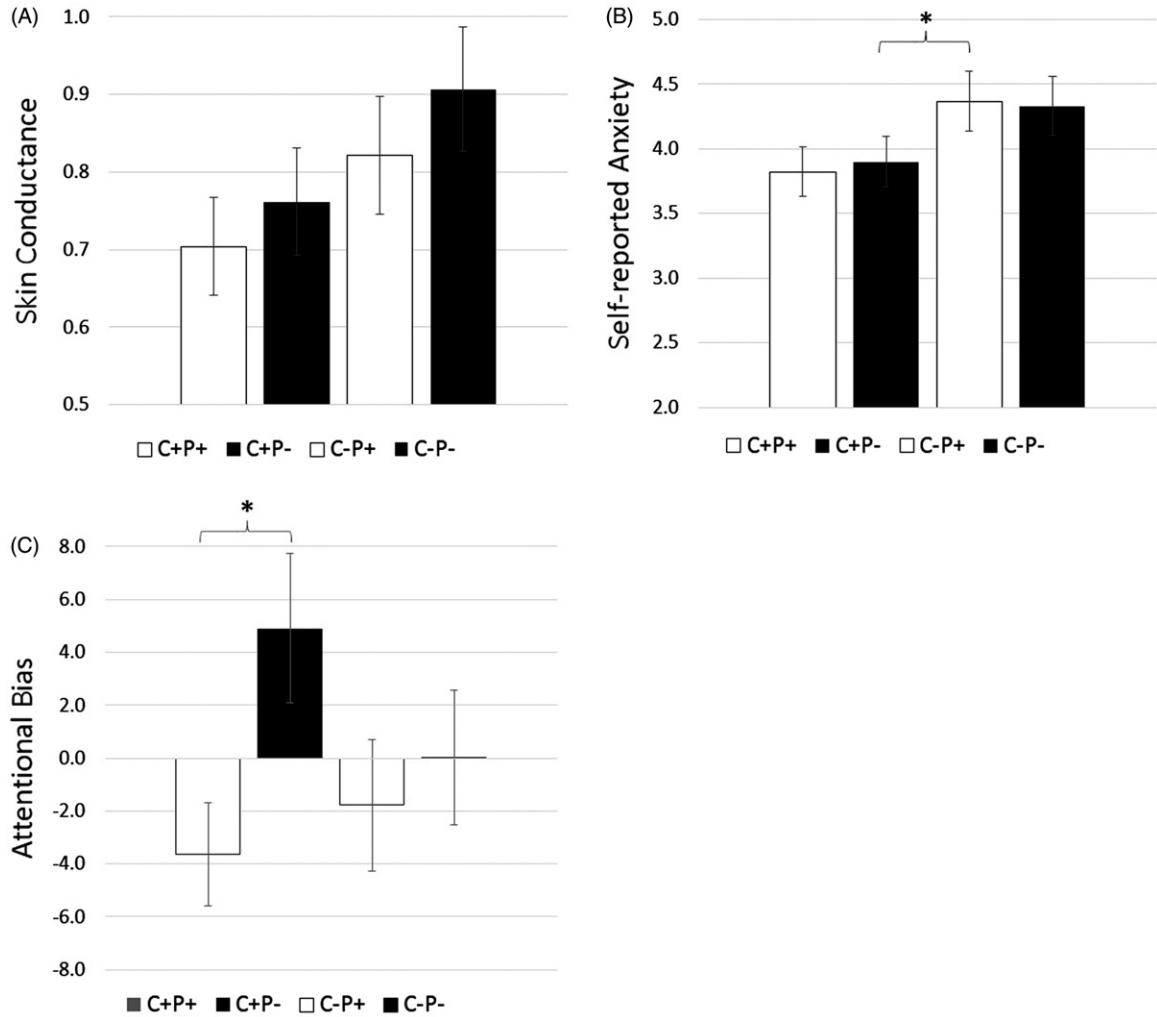

Figure 1. Depicted are mean and *standard errors of mean* for skin conductance (μmho) (A), self-reported anxiety (points) (B) and attentional bias (ms) (C) in the four conditions: controllable-predictable (C + P+), controllable-unpredictable (C + P−), uncontrollable-predictable (C − P+) and uncontrollable-unpredictable (C − P−). Significance levels: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ (Bonferroni corrected for multiple comparisons).

Table 2. Analysis of variance for skin conductance, self-reported anxiety and attentional bias.

	Skin conductance				Self-reported anxiety				Attentional bias			
ANOVA results	*F*	*df*	*p*	ηp^2	*F*	*df*	*p*	ηp^2	*F*	*df*	*p*	ηp^2
Main effects												
Control	10.80	75	**0.002**	0.126	22.22	75	**0.000**	0.229	0.83	75	0.338	0.012
Control*BAI	0.28	75	0.596	0.004	0.05	75	0.828	0.001	1.05	75	0.307	0.014
Control*BDI	0.73	75	0.397	0.010	0.27	75	0.604	0.004	1.49	75	0.226	0.019
Prediction	4.66	75	**0.034**	0.058	0.08	75	0.777	0.001	4.64	75	**0.034**	0.058
Prediction*BAI	0.09	75	0.764	0.001	0.00	75	0.951	0.000	0.00	75	0.995	0.000
Prediction*BDI	0.13	75	0.716	0.002	0.18	75	0.676	0.002	1.78	75	0.186	0.023
Control*Prediction	0.14	75	0.710	0.002	0.33	75	0.569	0.004	3.21	75	0.077	0.041
Control*Prediction*BAI	0.37	75	0.545	0.005	0.13	75	0.715	0.002	5.45	75	**0.022**	0.068
Control*Prediction*BDI	6.02	75	**0.016**	0.074	1.30	75	0.258	0.017	0.10	75	0.749	0.001
Time effects												
Time					1.51	75	0.223	0.020				
Time*BAI					2.15	75	0.147	0.028				
Time*BDI					0.26	75	0.612	0.003				
Control*Time					3.46	75	0.067	0.044				
Control*Time*BAI					0.18	75	0.676	0.002				
Control*Time*BDI					7.42	75	**0.008**	0.090				
Prediction*Time					0.51	75	0.477	0.007				
Prediction*Time*BAI					5.64	75	**0.020**	0.070				
Prediction*Time*BDI					1.15	75	0.288	0.015				

BAI = Beck Anxiety Inventory (BAI) median split, BDI = Beck Depression Inventory (BDI) median split.
Bold values indicate $p < 0.05$.

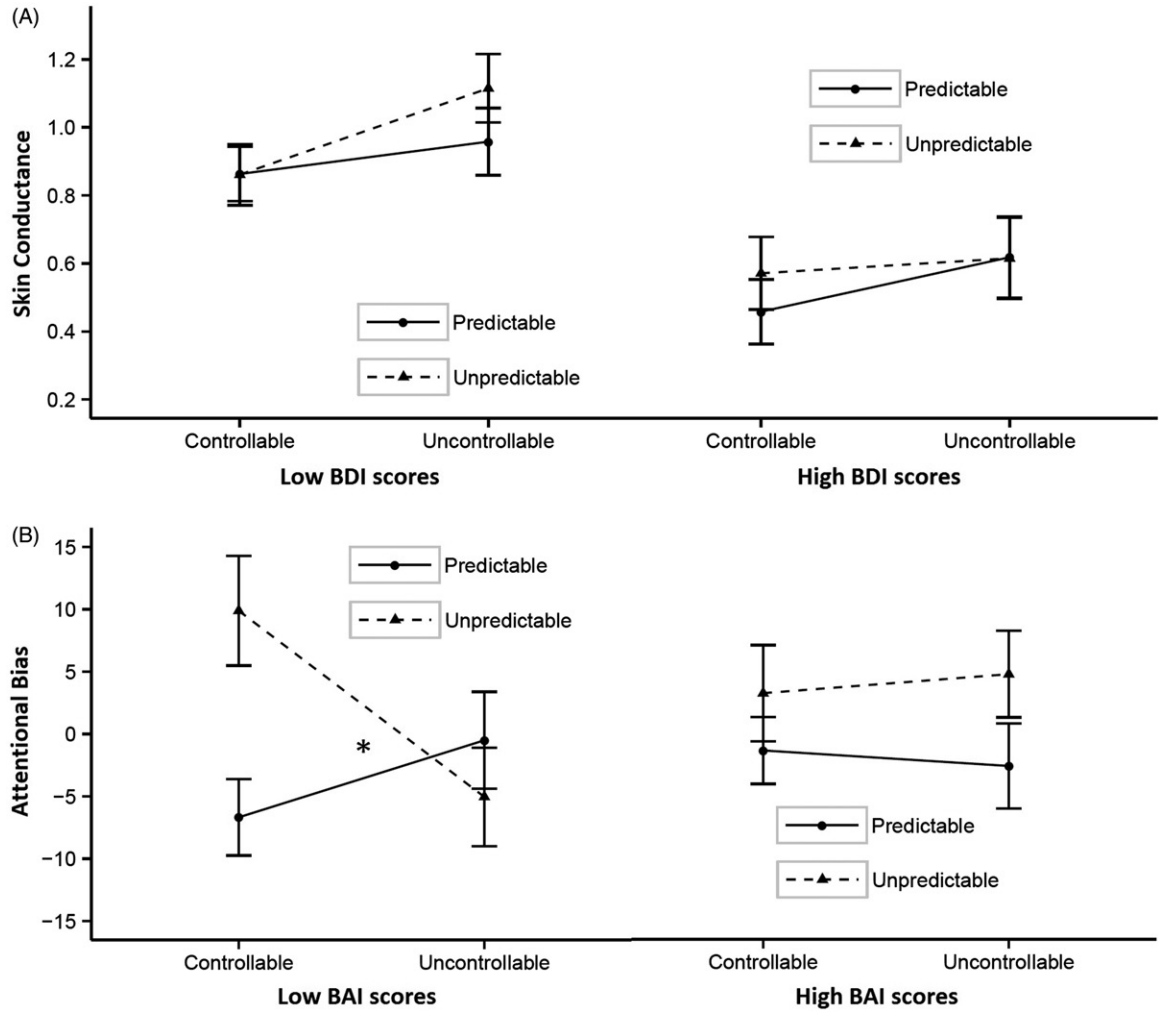

Figure 2. Significant three-fold interactions in skin conductance (μmho) for participants with low Beck Depression Inventory (BDI) scores and participants with high BDI scores (A) and in attentional bias (ms) for participants with low Beck Anxiety Inventory (BAI) scores and participants with high BAI scores (B). An additionally significant two-fold interaction in attentional bias is indicated with * (corrected for multiple comparisons).

observed a significant three-fold interaction of *controllability by predictability by BDI* in SC, two significant interactions of *controllability by BDI by time* and of *predictability by BAI by time* in self-reported anxiety, and an interaction of *controllability by predictability by BAI* in attentional bias (Table 2). The interaction for SC revealed that in participants with low BDI scores, shock unpredictability further increased SC in the uncontrollable condition, whereas in the controllable condition, shock unpredictability did not affect SC. In participants with high BDI scores, unpredictability did not increase SC in the uncontrollable condition, while it did additionally increase it in the controllable condition (Figure 2A). The interaction of *controllability by BDI by time* indicated that in participants with low BDI scores, the self-reported anxiety in both controllable and uncontrollable conditions decreased within test sessions, whereas in participants with higher BDI scores the self-reported anxiety in uncontrollable conditions increased within test sessions (Figure 3A). The interaction of *predictability by BAI by time* revealed that in participants with low BAI scores, the self-reported anxiety in both unpredictable and predictable conditions decreased within test sessions, while in participants with higher BAI scores the self-reported anxiety in unpredictable and predictable conditions did not decrease; on the contrary, the self-reported anxiety in the predictable conditions even showed a trend towards an increase in participants with higher BAI scores (Figure 3B). Finally, the interaction in attentional bias reflected that in participants with low BAI scores, only the uncontrollable-predictable condition (C – P+) elicited a positive attentional bias, while in participants with higher BAI scores, both unpredictable conditions elicited a positive attentional bias (Figure 2B).

Discussion

Studies simultaneously investigating controllability and predictability are rare in humans. Previous research mainly focused either on uncontrollability inducing feelings of helplessness and depression, or on unpredictability eliciting sustained anxiety. The few existing studies investigating the two factors simultaneously did not yield interaction effects (Baker & Stephenson, 2000). We hypothesized that they failed to find interactions because they did not factor in susceptibilities of participants. Therefore, we designed a paradigm enabling the distinct but simultaneous examination of the effects of uncontrollable and unpredictable stress (electrical shocks) on multiple anxiety measures (skin conductance, self-reported anxiety and attentional bias towards

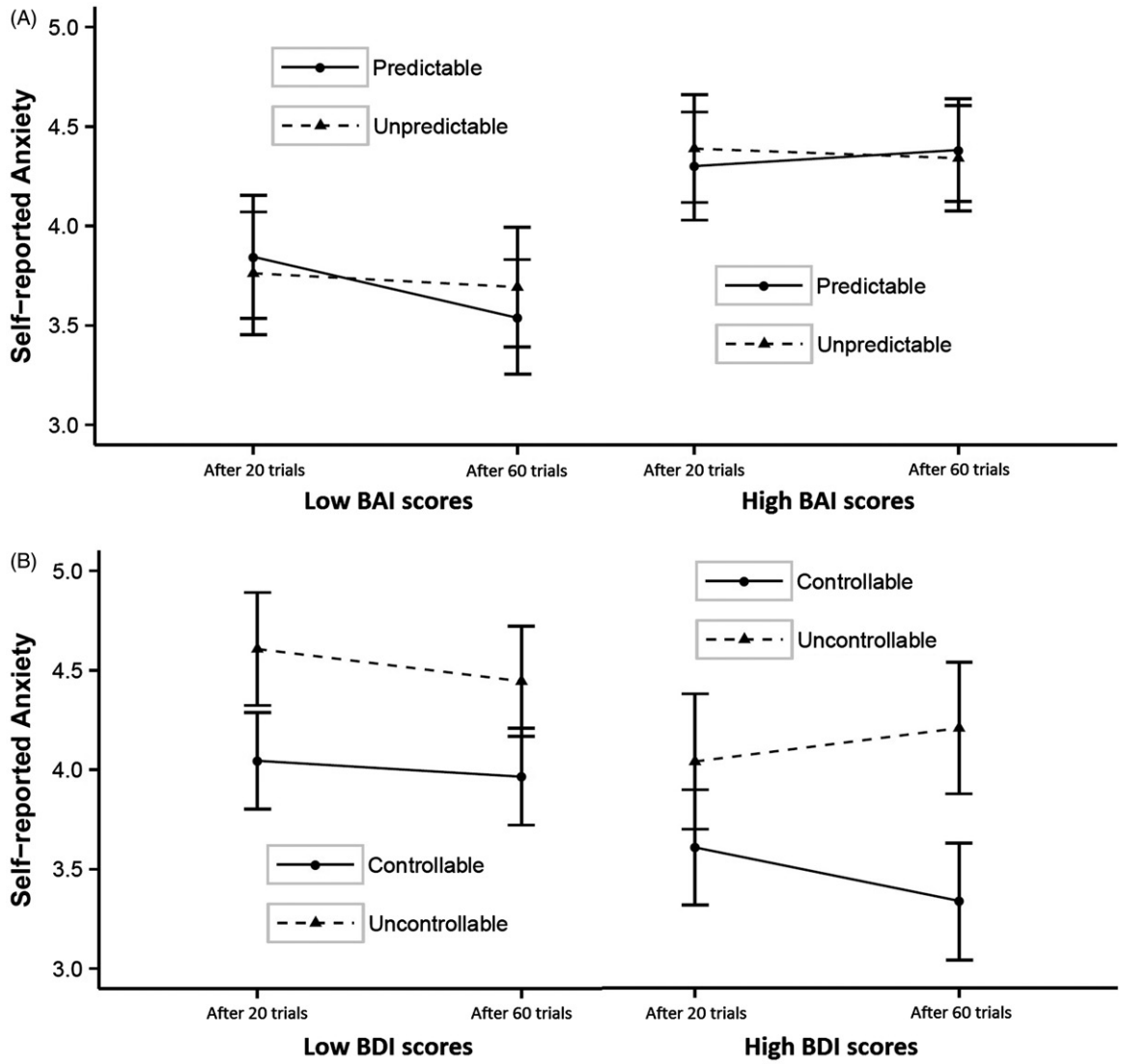

Figure 3. Significant three-fold interactions in self-reported anxiety (points) within test session (measured after 20 trials and after 60 trials) for participants with low Beck Anxiety Inventory (BAI) scores and participants with high BAI scores (A) and for participants with low Beck Depression Inventory (BDI) scores and participants with high BDI scores (B).

threat) in healthy participants stratified according to subclinical symptoms of depression (BDI) and anxiety (BAI). With this approach, we revealed not only separate main effects of *controllability* and *predictability*, but also interaction effects of the two factors with subclinical scores of depression and anxiety in all three anxiety measures. These findings may provide insights into the psychological mechanisms underlying a depressive/anxiety co-morbidity.

Concerning the separate main effects of *controllability* and *predictability*, we were able to replicate previous findings. Here, we demonstrate that conditions with uncontrollable shocks elicited increased physiological arousal and increased self-reported anxiety compared to conditions with controllable shocks. These findings are consistent with animal studies on learned helplessness (Azzinnari et al., 2014) reporting escape-deficits together with an increased anxiety of anticipated shocks when mice were administered uncontrollable stressors (compared to controllable stressors). Furthermore, previous studies in humans (Baker & Stephenson, 2000; Breier et al., 1987; Peters et al., 1998) also demonstrated task performance reductions and increases in heart rate reactivity when participants experienced uncontrollable stress experiences. Regarding predictability, we found increased physiological arousal as well as higher attentional biases towards threat in conditions with unpredictable shocks in contrast to conditions with predictable shocks. These findings are in line with multiple studies by Grillon (2004) and Mol et al. (2007) demonstrating that healthy participants revealed increased startle reflexes as an index of increased sustained anxiety in situations with unpredictable compared to predictable stressors. In addition, this is also consistent with translational evidence showing that even unpredictability *per se* (without any threat) induces anxiety-like behavioral and neural effects in humans and mice (Herry et al., 2007).

Previous research has demonstrated that depressed participants, compared to healthy controls, felt more helpless and showed more altered information processing when confronted with uncontrollability (Diener et al., 2009). Similarly, high anxious individuals as well as patients with panic disorders and post-traumatic stress disorders showed elevated startle magnitudes in unpredictable stressor situations compared to

healthy controls (Glotzbach-Schoon et al., 2013; Grillon et al., 2008, 2009). Consistent with these studies, we found interactions of depression traits (BDI) with *controllability* and interactions of anxiety traits (BAI) with *predictability* in self-reported state anxiety. More specifically, we demonstrated that in participants with low BDI scores, the self-reported anxiety in both controllable and uncontrollable conditions decreased within test sessions, while the self-reported anxiety in the uncontrollable conditions increased within test sessions in participants with higher BDI scores. This finding is plausible if we base its interpretation on the learned helplessness model (Seligman, 1975). Accordingly, participants with low BDI scores might have more frequently experienced control over their life circumstances, which immunized them against the effects of the experimentally implemented uncontrollability. This interpretation is supported by findings demonstrating that after experiencing a loss of control, depressed patients (in contrast to healthy controls) continued to feel helpless after control had been reinstated (Diener et al., 2009). Regarding predictability, we found that in participants with low BAI scores, self-reported anxiety in both the predictable and the unpredictable conditions decreased within test sessions, whereas this decrease of anxiety was not seen in participants with higher BAI scores. On the contrary, self-reported anxiety in the predictable conditions slightly increased within test sessions in high anxious individuals. These results are supported by research on fear and anxiety learning, which demonstrates that in high anxious individuals both fear and anxiety associations are acquired faster and remain more stable over time than in healthy controls (Barrett & Armony, 2009; Sehlmeyer et al., 2011).

Stratifying our participants into groups with low vs. high depression and low vs. high anxiety scores revealed significant interaction effects of *controllability, predictability* and BDI for SC and of *controllability*, *predictability* and *BAI* for attentional bias. More precisely, in participants with low BDI scores, unpredictability further increased physiological arousal only in the uncontrollable but not in the controllable condition. In participants with high BDI scores, on the other hand, unpredictability did increase arousal in the controllable condition, while it did not additionally affect it in the uncontrollable condition. It must be highlighted that the lower overall physiological arousal level in participants with higher BDI scores compared to participants with low BDI scores (Figure 2A and Table 1) seems to be a characteristic finding in depressed individuals, which has been reported on multiple occasions (Allen et al., 1999; Mardaga & Hansenne, 2009; McTeague et al., 2009; Thorell, 2009). Because of this, we restricted the interpretation of this finding to the relative effects of uncontrollability and unpredictability. There is, to the best of our knowledge, no previous research on the interaction of control and prediction with (sub-)clinical symptoms but our findings can be interpreted in light of the learned helplessness theory again. Assuming that participants with higher BDI scores have previously experienced helplessness, exposure to unpredictable shocks might be sufficient to induce a feeling of helplessness leading to heightened arousal even if shocks are controllable (in C + P−) (Diener et al., 2009). In contrast, participants with low BDI scores might have low susceptibility to helplessness, and unpredictability of shocks only increased arousal when shocks actually were uncontrollable (in C − P−). Based on these results, we believe that previous studies did not find interaction effects of controllability and predictability because they did not take participants' depression or anxiety trait scores into account.

Moreover, we demonstrate that both participants with low and participants with higher anxiety (BAI) scores showed negative attentional biases in the predictable conditions. However, in participants with higher BAI scores both unpredictable conditions elicited a positive attentional bias, whereas participants with low BAI scores only displayed a positive attentional bias in the uncontrollable-predictable condition (C − P+). To interpret these findings two things must be added: first, the reported attentional biases were calculated from no-danger trials to compare attentional biases towards threat as an indicator of anxiety without confounding danger cue induced fear. Additionally, comparing attentional biases in danger trials did not reveal any significant interaction effects ($p > 0.05$). Second, negative attentional biases are generally seen as a coping mechanism of turning the attention away from threat in situations with aversive but not highly threatening stimuli (Cooper & Langton, 2006). In light of this, we speculate that in predictable conditions, both low anxious and high anxious individuals regulated their emotions in no-danger trials by turning their attention away from angry faces knowing that these trials signify periods of safety (Grillon, 2002). In unpredictable conditions, on the other hand, participants had no periods of safety which led to sustained anxiety and positive attentional biases towards angry faces. Using this interpretation, the question remains why participants with low BAI scores still showed a negative attentional bias in the uncontrollable-unpredictable condition. However, it might be the case that these low anxious individuals comprehended (either consciously or subconsciously) that they could neither control nor predict shocks in this condition and thus turned to another emotion regulation strategy instead, whereas high anxious individuals failed to adapt such a strategy.

Our study has some limitations. The major limitation is that shock controllability was confounded with shock intensity in our experimental paradigm. Even though, all participants received the exact same number and same intensity of shocks (due to the within-subject design), the intensity of shocks was always lower in controllable compared to uncontrollable conditions in order to elicit the impression of control during controllable conditions. Previous studies admittedly demonstrated that subjective controllability had similar ameliorating effects on anxiety of pain and on pain perception (Salomons et al., 2004) as did actual objective controllability. However, by using objective controllability in our study, we cannot rule out that the confounded shock intensity may have exaggerated the effects of uncontrollability in this experiment. For example, by examining the relative importance of the two factors on SC (C − P− > C − P+ > C + P− > C + P+), we found that controllability appears to have a greater impact on physiological arousal than predictability. However, this finding may be specific for our experimental design given that the implementation of controllability enabled the participants to

ameliorate the aversive shocks, while predictability did not. Future studies should thus employ experimental designs allowing the combination of subjective controllability with predictability to avoid confounds with stressor intensity. Another limitation concerns our implementation of predictability. We modeled our experimental design based on Grillon's concept of predictability (Grillon et al., 2004; Mol et al., 2007). However, his concept of predictability slightly differs from the definition of predictability used in animal research. For instance, in our study, participants were explicitly informed about the imminent conditions, whereas rodents had to learn themselves which conditions are predictable or unpredictable. Additionally, in our predictable conditions, participants had to discriminate between cues signaling danger and cues signaling safety. Animals, in contrast, are usually only confronted with one signaling stimulus. These differences between human and animal research have to be considered when our results are interpreted. Furthermore, because we investigated healthy participants, we could not use clinical cut-offs to stratify our participants into groups of low vs. clinically relevant BDI/BAI scores. Using median splits to stratify our sample, however, might have led to arbitrary cut-offs, so that our interaction results are likely not easy to replicate. Because of this, future studies should examine clinical samples applying clinically relevant cut-offs. Finally, we assumed in our interpretations that participants with higher depression scores also felt more helpless in the experiment and in their life circumstances. However, we did neither specifically assess their experimentally induced nor their general feelings of helplessness. Future studies should systematically assess feelings of helplessness during the experiment.

Conclusion

In conclusion, we provide evidence that uncontrollability and unpredictability of stressors have separate but also interacting effects on several anxiety measures in participants stratified according to subclinical scores of depression and anxiety. Previous research has already established that uncontrollable stress can elicit feelings of helplessness and depression, while unpredictable stress facilitates the emergence of sustained anxiety. However, our results reveal a more complex picture when the two factors are combined. Of course, our findings are preliminary at this point but they may turn out to be relevant considering the frequent co-morbidity of major depression and anxiety disorders. Stressful life experiences are often uncontrollable and unpredictable at the same time. According to our results, individuals who, for example, already suffer from depression may be more susceptible to develop anxiety disorders in the face of stressors that are both uncontrollable and unpredictable. Neurobiological studies in animals suggest that such interactions might be processed in neural circuits involving connections between the amygdala and the dorsal raphe nucleus. Future studies could test this hypothesis using neuroimaging and a similar experimental paradigm as ours in clinical samples consisting of patients with depression, patients with anxiety disorders and patients with a depressive/anxiety co-morbidity. Additionally, epidemiological studies could examine the effects of stressful life experiences that are both uncontrollable and unpredictable in the development of co-morbid depression and anxiety disorders.

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