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The Psychology of HPA Axis Activation: Examining Subjective Emotional Distress and Control in a Phobic Fear Exposure Model

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Abstract

The HPA axis plays a key role in mediating the effects of “stress” on health, but clarifying mechanisms requires an understanding of psycho-biological linkages. There has long been an implicit assumption that subjective emotional distress (e.g., fear) should activate the HPA axis. Although this assumption was challenged 25 years ago (Curtis, 1976), laboratory studies in humans are limited. In this study we sought to replicate Curtis’ findings and extend it by investigating if presence or absence of stressor control shapes HPA axis reactivity in a phobic fear exposure model. We recruited 19–45-year-old specific phobia participants ($n = 32$ spider/snake phobia; $n = 14$ claustrophobia) and gradually exposed them to their feared object or situation while measuring hormonal (ACTH and cortisol) and subjective (emotional distress, perceived control) responses. Utilizing a dyadic yoked design, we compared HPA reactivity when the pace of exposure was controlled by participants to identical exposure given to matched participants in the absence of control. Results showed that phobic fear exposure generated intense emotional distress without a corresponding increase in HPA axis activity. Although our actual manipulation of control failed to impact HPA responses, *perceived* control during exposure was associated with lower cortisol, an effect that was moderated by actual availability of stressor control. Our findings replicate Curtis’ findings and challenge the still common but unsupported assumption that HPA axis activity reflects subjective distress. These results also highlight the importance of both perceived and actual aspects of stressor control in understanding what is truly “stressful” to the HPA axis system.

Keywords

cortisol; ACTH; fear; exposure; phobia; control; stress context

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1. Introduction

Stress is a complex construct that has been studied for decades, by many disciplines, but it remains poorly understood despite its clear relevance to health and disease (McEwen, 2008). Much biological work has focused on the hypothalamic-pituitary-adrenal (HPA) axis, which shapes biobehavioral responses to acute stressors, but also facilitates long-term adaptations to repeated challenges (Chrousos, 2009), perhaps by adjusting neural “set points” in response to developmental experience, with potential consequences for psychopathology (de Kloet et al., 2005; Lupien et al., 2009; Meaney et al., 2007). Stress has frequently been defined by subjective experience, with negative emotional states (fear, anxiety, and distress) being common markers associated with ill health (Clarke and Currie, 2009). Understanding the magnitude of stress one experiences is often important, and we almost universally rely on the individual’s subjective experience as an indicator of stress that they are exposed to. The common implicit assumption is that subjective and neuroendocrine stress responses are two sides of the same coin – that subjective stress is also biological stress. Empirical support for this assumption, however, is weak, creating uncertainty about what psychological factors to target if we want to reduce the detrimental health consequences of stress.

Studies explicitly investigating the covariance between subjective-emotional and biological indices of stress have produced inconsistent results. Some positive links have been seen between emotional responses and HPA axis reactivity (Al’Absi et al., 1997; Oldehinkel et al., 2011; Oswald et al., 2004; Schlotz et al., 2008), but effect sizes were small (e.g., Oldehinkel et al., 2011), and depended on stressor type (e.g., Al’Absi et al., 1997; Oswald et al., 2004) and analytical approach (Schlotz et al., 2008). Other studies did not find links between subjective and neuroendocrine stress measures. The common assumption that negative affect should activate the HPA axis was challenged decades ago, using a phobic fear exposure model that generated intense emotional distress without a corresponding increase in HPA axis activity (Curtis et al., 1976; Curtis et al., 1978). Other data have replicated these results using exposure paradigms with specific phobias (Diemer et al., 2016; Lass-Hennemann and Michael, 2014; Van Duinen et al., 2008) and other anxiety disorders (Gustafsson et al., 2008; Kellner et al., 2012; Siegmund et al., 2011), though not consistently (Alpers et al., 2003; Schumacher et al., 2014). Considerable additional work has further confirmed the disconnect between subjective distress and cortisol release, using pharmacological (Abelson et al., 2008) and social-evaluative challenge tasks (Abelson et al., 2014; Cohen et al., 2000; Shiban et al., 2016). Systematic and meta-analytic reviews have further supported the lack of clear links between subjective distress and HPA axis activity both in field (Hjortskov et al., 2004) and laboratory studies (Campbell and Ehler, 2012; Dickerson and Kemeny, 2004). Stress can be bad for health (McEwen, 2008), and the HPA axis mediates some portion of the “damage” (Chrousos, 2009), but if emotional distress is not linked to HPA axis activation and therefore not an appropriate focus for stress reduction interventions, the question arises what other factors might be salient to the HPA axis and thus could be targeted.

The phobia studies by Curtis and colleagues (1976; 1978) provided a first clue. Intense subjective distress generated by fear exposure did not elicit corresponding cortisol responses, but the novelty of entering the laboratory did, even in the absence of significant

subjective impact. The highest cortisol levels occurred at entry into the experimental context, and these initial elevations declined with repeated visits. Subsequent work has confirmed that contextual factors like novelty/familiarity, lack of or access to control or coping responses, and availability of social support are more closely linked to HPA axis activation or moderation than subjective distress per se. For example, novelty robustly activates and familiarity reduces cortisol release in animals (Hennessy et al., 1995) as well as humans (Davis et al., 1981; Peters et al., 2011). Lack of stressor controllability and social evaluative threat are potent and reliable activators of human HPA axis activity (Dickerson and Kemeny, 2004). Social evaluative threat may be particularly potent because it is inherently uncontrollable. In contrast, social support can dampen cortisol reactivity (Cosley et al., 2010; Kirschbaum et al., 1995), perhaps because access to help facilitates coping and control responses (Levine, 2000). Experimental manipulations of novelty, control, and coping can reduce HPA axis reactivity to direct *pharmacological* activation (Abelson et al., 2008; Abelson et al., 2010) suggesting that these factors are highly salient to the HPA axis. The Trier Social Stress Test (TSST) has been a primary stress paradigm for studying *psychosocial* HPA axis activation in humans and in identifying this system's sensitivity to social-evaluative threat and uncontrollability (Dickerson and Kemeny, 2004). However, its design does not lend itself to efforts to dissect the independent and specific effects of emotional distress and threat uncontrollability.

The aim of this study was to separate fear-related distress from threat controllability, to determine whether fearful distress itself triggers cortisol release and how it might interact with stressor controllability in shaping HPA responses. We utilized a design that built upon two old but seminal studies showing that intense fear, by itself, did not elicit a cortisol response (Curtis et al., 1976; Curtis et al., 1978). In the primary experiment we studied people with two specific phobias (spiders/snakes) during exposure to their feared object, using a dyad-yoked design that isolated the experience of “control”, while trying to equate levels of fear. We hoped to replicate the prior finding (Curtis et al., 1976; 1978) that intense fearful distress generated by phobic fear exposure does not by itself trigger HPA axis activity and test the hypothesis that fearful distress coupled with lack of control over the threat might do so. However, because human use restrictions precluded direct exposure of participants to uncaged spiders or snakes, reducing the ecological validity of the exposure and the degree of uncontrollability we could create, we added a follow-up study using participants with a fear of enclosed spaces (claustrophobia). This provided exposure opportunities (using a mock MRI scanner) in which the experience of lack of control could be more directly imposed and the sensation of loss of control (e.g., feeling trapped) might be particularly intense (Shafran et al., 1993).

2. Methods

2.1 Design

After accommodation, participants with specific phobias underwent graded exposure to their feared animal. Experimentally yoked dyads received identical “doses” of exposure, with one participant within each dyad having control over exposure pace (+Control) by dictating the timing with which the feared animal was brought closer, while their matched “partner” was

administered exposure “without experimental control” (–Control) over exposure pace. We examined the impact of control on hormonal and subjective responses to exposure, as well as subjective distress-hormonal linkages. All procedures were approved by the Institutional Review Board (IRB).

2.2 Participants

Physically healthy specific phobia participants were recruited through multi-media advertising. After phone screening, individuals received a face-to-face screening to assess clinical, self-report, and behavioral measures. Qualifying participants were 18–45 years old (mean 22 ± 4.6), medically healthy, within 30% of ideal body weight (BMI mean 23 ± 2.8), with no recent exposure to psychotropic medication, no history of substance dependence or recent abuse (6 months), low levels of alcohol and tobacco use (mean 1.3 ± 1.7 drinks/week; all participants were non-smokers), negative urine drug screens, and normal laboratory blood counts to rule out anemia and infection. Participants were diagnosed with a specific phobia of snakes or spiders (as determined by DSM-IV criteria), using a full SCID interview. They had no SCID confirmed current psychiatric comorbidity and no family history of bipolar disorder or psychosis. Females were premenopausal, not pregnant or lactating, not using birth control pills, and studied within 10 days after onset of menses to preclude the possibility of pregnancy and control for the effects of sex hormones on the HPA axis (for an overview regarding the role of age and gender, sex steroid levels, pregnancy, lactation and breast-feeding on cortisol responses to acute stress, see Kudielka et al., 2009). Participants signed written consent and were paid \$200 for the completion of the neuroendocrine study procedures. Six participants were excluded (3 due to missing hormonal values, 1 due to belatedly discovered excessive drinking, and 2 (+Control/unmatched subjects) due to extreme behavioral phobic fear (2 SD above group means), yielding a final sample of 32 participants.

2.3 Overview of Procedures

Following the screening visit, participants had two approximately 3-hour study visits. Visit 1 (Accommodation Day) allowed them to get comfortable with the research procedures. Participants reported at 1300h and intravenous (IV) access was established no later than 1330h, using an 18–20 gauge angiocatheter in an antecubital vein, kept open with a normal saline drip. They then rested until 1600h (with light reading to pass the time) – knowing that no exposure would take place. Hormonal and subjective data were obtained with the same frequency and timing as planned for their exposure day. Visit 2 (Exposure Day) took place within 10 days of visit 1. Initial procedures were identical, including IV insertion and a 1 hour resting period in the accommodation room. Participants then listened to taped instructions at 1425h. Pre-exposure blood samples were drawn at 1400h and 1425h (30 and 5 minutes prior to exposure start). Participants then moved to a second room and the 60-minute exposure began around 1430h, with blood sampling at 15, 30, 45, 60 minutes post exposure initiation. During exposure, the animal (in a closed aquarium) was moved gradually closer over 6 stations. Additional ACTH samples were obtained 5 minutes after the animal was moved one station closer to capture acute responses to the approaching animal (“station move samples”). After exposure, participants returned to the

accommodation room (30-minute recovery period), with hormonal sampling at 75 and 90 minutes post exposure initiation.

2.4 Measures

2.4.1 Clinician rating—The SCID interviewing clinician rated participant's phobic severity using the Clinical Global Impressions (CGI) Scale (0 = Normal; 13 = Extremely severe).

2.4.2 Subjective measures—During screening, participants completed a questionnaire specific to their fear (Spider or Snake Phobia Questionnaire; Klorman et al., 1974). We used a standard SUDs scale (Subjective Units of Distress; 0 = no distress whatsoever, completely calm and relaxed; 100 = maximal distress/fear/anxiety imaginable) at baseline (30, 5 minutes prior to exposure), during exposure (every 2.5 minutes at a given station and 25 seconds after each station move; ratings were averaged over 15 minute intervals), and during recovery (75, 90 minutes post exposure initiation). Subjective states were also recorded using Visual Analog Scales (VASs; 100-mm visual analog lines anchored from “not at all” to “extremely”). VAS of subjective distress (mean ratings of “anxious”, “nervous”, “fearful”) was measured at baseline (60, 30, 5 minutes prior to exposure), during exposure (30, 60 minutes post exposure initiation) and during recovery (75, 90 minutes post exposure initiation). VAS of perceived control (“To what degree do you believe you are able to control what happens to you during this experiment?”) was also measured on 100-mm visual analog lines (anchored from “not at all” to “extremely”) and assessed at baseline (60, 30 minutes prior to exposure), during exposure (30, 60 minutes post exposure initiation) and during recovery (90 minutes post exposure initiation).

2.4.3 Behavioral Avoidance Test (BAT)—To quantify phobic avoidance, a Behavioral Avoidance Test (BAT) was administered during screening. The BAT utilized 6 stations, each marked on the floor, except for Station 1, which was right outside of the room. The animals (an approximately 5-foot snake or a 4–5-inch tarantula) were within covered glass aquariums. Stations 2 to 5 brought the animal closer at approximately 5 foot intervals until it was directly in front of participants (Station 5), with the final Station 6 asking participants to put their hands on the glass. Participants were asked to allow the animal to be brought closer over the 6 marked stations as rapidly as possible, to the closest station they could tolerate. They had 30 seconds at each station to determine whether they could tolerate the next step. The test ended the moment 30 seconds elapsed at a given station without willingness to accept the next station move (duration thus ranged from 30 seconds, if they would not let the animal to enter the room, to 3 minutes if they completed all 6 stations). We recorded the closest station achieved and VAS fear ratings (anxious, fearful, and distressed) at each station.

2.4.4 Hormonal measures—Serum ACTH and serum levels of cortisol were determined by a chemiluminescent enzyme immunoassay (IMMULITE) according to the manufacturer's directions (Siemens Healthcare Diagnostics Inc., USA). Inter-assay and intra-assay variations were less than 8% and 6% respectively.

2.5 Procedures

2.5.1 Matching procedure—Dyads were created using the following matching criteria: Same phobia type, age (± 5 years), sex, and phobic severity as determined by clinician rating (± 1 point on the CGI Scale), self-report (± 1 SD on the Spider/Snake Phobia Questionnaire), and behavioral avoidance (BAT: $\pm$ one station of each other in closest station achieved and ± 15 points on VAS fear ratings at each station). In order to determine a severity appropriate exposure pace, +Control participants were always run first, so random assignment was not possible. We then sought new participants who were “matching” to a completed +Control participant, expecting similar distress responses to identical exposure dosage. New matching participants were run in the –Control group. New participants who did not match were added to the +Control group, providing an expanding pool of +Control participants for the subsequent matching search. Not all +Control participants were ultimately matched, providing a third group, called +Control/unmatched.

2.5.2 Experimental manipulation of control—Participants received tape recorded instructions 5 minutes prior to exposure. Both groups were given a brief rationale for exposure therapy, emphasizing that through repeated exposure, fear and avoidance would reduce. Participants in the +Control group were encouraged to allow rapid approach, but they were assured that they had ultimate control over the pace of the exposure and that the animal would never be moved closer without their explicit permission. Participants in the –Control group received identical instructions, except they were told that the therapist would be informing them when it is time to move the animal closer.

2.5.3 Exposure procedure—Exposure was conducted by an experienced cognitive-behavioral therapist in the same context as the screening day BAT. The same therapist executed sessions for both participants in a matched dyad. Identical to the BAT, the animal began outside the room (Station 1) and gradually moved closer until it was in front of participants with their hands on the glass (Station 6). The therapist provided standardized therapeutic support to both groups (e.g., “You can do it,” “Let yourself feel the anxiety and it will diminish”). In the +Control group, the therapist asked at set intervals if participants would allow the animal closer, with reminders that moving closer was therapeutic, but would only be done when the participant felt ready. The most rapid permitted pace was one step closer every 5 minutes. A “map” of each +Control participant’s exposure pattern was created by recording the time of each station move. Their matched –Control “partner” received the exact same exposure experience (time and distance), except it was imposed on them by the therapist with no requests for consent. They were simply told that the animal was being moved closer, with a simultaneous physical move to the next station and a verbal announcement of that move (“The protocol requires me to move to the next station”). They were not given any warnings prior to the move, so there was an element of unpredictability as well as uncontrollability. The groups thus received identical exposure, but differed in ability to control the exposure pace.

2.6 Claustrophobia Sample

We also recruited participants with a phobia of enclosed spaces (claustrophobia). Recruitment and screening procedures were identical to the spider/snake phobia sample,

except that we assessed phobic severity with the Claustrophobia Questionnaire (CLQ; Radomsky et al., 2001) and measured behavioral and imaginative avoidance in a mock MRI scanner (parallel to the animal BAT procedures, using the claustrophobic context that would be used on the exposure day). Claustrophobic participants were more difficult to recruit, partly because they are less prevalent (Stinson et al., 2007), but also because co-morbid anxiety disorders, an exclusion criterion, are more common (Depla et al., 2008). We consequently relaxed the rather stringent matching criteria utilized in the animal phobia sample to facilitate yoking. Nevertheless, all yoked dyads were sex-matched, within 6 years of age, and of comparable claustrophobic severity as determined by clinician rating (± 4 points on the CGI Scale), self-report (CLQ scores within the normative range of the claustrophobic population), and avoidance responses (BAT: ± 25 points in average VAS fear ratings). We obtained a preliminary sample of 7 matched dyads ($n = 14$; one participant was excluded from ACTH analyses and another one was excluded from cortisol analyses, due to multiple assay outliers). Compensation was \$200. Study procedures and experimental manipulation of control were identical to those described for the animal phobia sample, except that the phobic stimulus was a mock MRI scanner. During the 60-minute exposure, claustrophobic participants gradually moved further into the scanning tube over 6 predetermined stations of increasing challenge. Station 1 had participants lying on the scanner gurney fully outside of the scanning tube. At station 2, they were moved into the scanner tube to their shoulders (head alone inside). At station 3, the head and upper body (to the hips) were inside the tube. At station 4, they were moved in as far as the gurney allowed (for most participants this left just feet, ankles and maybe calves outside). At station 5, the head-end scanner opening was covered with a dark cloth. At station 6, the foot-end scanner opening was also covered with a dark cloth, leaving participants in a dark and enclosed space that many described as a “tomb.” The therapist conducted exposure with the +Control and –Control dyads exactly as described earlier for snake and spider phobias.

2.7 Statistical Analyses

Hormonal time series were analyzed using RM-ANOVAs with particular interest in group-by-time interactions. We also used t-tests on calculated measures to quantify group differences or within-person changes at baseline (mean of pre-exposure samples at –30 and –5 minutes), during exposure (mean of exposure samples at +15, 30, 45, and 60 minutes), at peak (individually selected maximum levels during exposure), as well as during accommodation (averaging over the +15, 30, 45, and 60 minute accommodation time points that corresponded to the measurement time points during phobic exposure). Subjective responses were analyzed similarly. SPSS version 24 was used for all statistical analyses.

3. Results

3.1. Animal Phobia Results

3.1.1. Effects of phobic fear exposure—Our first aim was to replicate findings that phobic fear does not elicit HPA axis responses despite intense emotional distress (Curtis et al., 1976; 1978). Paralleling the original work (Curtis, personal communication), we examined participants with control, combining our +Control and +Control/unmatched

groups, which were comparable in demographic and phobic severity measures (all p s $> .10$; see Table 1). This created an enlarged +Control group ($n = 21$).

Subjective distress, as measured in SUDs, rose dramatically in response to exposure, increasing more than three-fold from baseline to mean exposure levels ($t(20) = -12.18, p < .001$; see Table 1), with peak levels increasing about five-fold ($t(20) = -13.81, p < .001$). SUDs during exposure also exceeded levels at corresponding time points during accommodation ($t(20) = -9.51, p < .001$), but were comparable to fear ratings obtained during the BAT ($t(20) = 0.45, p = .658$). Subjective distress, as measured in VAS ratings, paralleled the verbally reported sharp increase (all p s $< .001$). Despite the substantial rise in distress with exposure, there was no corresponding increase in **ACTH or cortisol**. Indeed, hormonal levels declined significantly from baseline to mean levels during exposure (ACTH: $t(20) = 3.07, p = .006$; Cortisol: $t(20) = 3.22, p = .004$), as is typical during the afternoon phase of the normal diurnal rhythm in the absence of activation. Peak levels during exposure did not exceed baseline levels (ACTH: $t(20) = 1.61, p = .123$; Cortisol: $t(20) = 0.26, p = .797$), despite the five-fold increase in peak distress ratings. Notably, hormonal levels were higher during the first laboratory visit than they were during phobic fear exposure (ACTH: $t(19) = 2.11, p = .048$; Cortisol: $t(20) = 2.20, p = .039$). Hormonal and subjective distress (SUD or VAS) measures at baseline, during exposure, at peak, or in peak response (peak minus baseline) were not significantly correlated (all p s $> .10$). In summary, traditional phobic exposure conducted with participant control over the exposure pace elicited strong subjective distress without corresponding increases in HPA axis activity.

3.1.2. Effects of control—We then tested the effects of our control manipulation, using the experimentally yoked dyads who received identical exposure but differed in level of control over exposure pace. Matched dyads did not differ in demographic or phobic severity measures (all p s $> .10$; see Table 1), confirming that our yoking procedure was successful. As expected, VAS ratings of perceived control during exposure was higher for participants with control, relative to those without experimental control over the exposure pace ($t(21) = 3.10, p = .005$). However, participants with control also had greater perceived control *prior* to exposure relative to those without control ($t(21) = 2.12, p = .046$). This was also prior to introduction of the control manipulation, so it likely was a coincidental consequence of the fact that we did not use random assignment to groups (because the design prioritized matching on phobic severity in order to equilibrate subjective distress during exposure across the two groups).

Subjective distress, as measured by SUDs, changed over time (time $F_{7,147} = 41.03, p < .001$), with no group differences (group $F_{1,21} = 0.63, p = .44$, group $\times$ time interaction $F_{7,147} = 0.31, p = .95$), confirming that our yoking procedure yielded groups of comparable subjective distress. The time effect reflected a rise from baseline to mean SUDs during exposure ($t(22) = -10.28, p < .001$). VAS ratings of subjective distress closely mirrored these findings. SUDs data for all participants are presented in Figure 1.

ACTH and cortisol changed over time (ACTH: time $F_{7,147} = 4.08, p < .001$; Cortisol: time $F_{7,147} = 11.82, p < .001$), with no group differences (ACTH: group $F_{1,21} = 0.35, p = .56$, group $\times$ time interaction $F_{7,147} = 0.28, p = .96$; Cortisol: group $F_{1,21} = 1.89, p = .18$, group $\times$

time interaction $F_{7,147} = 0.33, p = .94$). Hormonal levels in both groups declined over time, falling significantly from baseline to mean exposure levels (ACTH: $t(22) = 2.49, p = .021$; Cortisol: $t(22) = 3.90, p = .001$). Hormonal data for all participants are presented in Figure 2.

As reported above, hormones declined within the +Control group, despite substantial elevations on subjective distress. Likewise, within the –Control group examined separately, there were substantial elevations in subjective distress (SUD and VAS; all $ps < .05$), but phobic fear, even in the absence of control, did not elicit hormonal reactivity (in fact, there was a trend that hormones declined from baseline to mean exposure levels; ACTH: $t(10) = 1.47, p = .17$; Cortisol: $t(10) = 2.22, p = .051$).

Above analyses excluded participants in the +Control/unmatched group, to take full advantage of the dyadic design that most stringently isolated the effects of control. However, the +Control/unmatched group did not differ in any meaningful way from the matched +Control group, and including it enhances power. Our manipulation of control significantly increased perceived control from right before exposure (min 30 minutes) to peak levels during exposure in the +Control group ($t(20) = -2.92, p = .008$), while perceived control in the –Control group remained low ($t(10) = -1.23, p = .25$). We conducted a final set of analyses that compared the enlarged +Control group to the –Control group. As before, SUDs increased in response to exposure, with no group differences (see Figure 1; time $F_{7,210} = 58.47, p < .001$, group $F_{1,30} = 0.29, p = .60$, group $\times$ time interaction $F_{7,210} = 0.43, p = .88$). Despite this rise in distress, ACTH and cortisol levels declined over time (see Figure 2; ACTH: time $F_{7,210} = 6.15, p < .001$; Cortisol: time $F_{7,210} = 12.13, p < .001$). The enlarged +Control group did not differ in hormone levels or responses from the –Control group (see Figure 2; ACTH: group $F_{1,30} < 0.001, p = .99$, group $\times$ time interaction $F_{7,210} = 0.30, p = .95$; Cortisol: group $F_{1,30} < 0.001, p = .99$, group $\times$ time interaction $F_{7,210} = 0.47, p = .86$), mirroring results with the matched dyads.

As a final test of capacity for HPA reactivity within specific phobics, we examined ACTH responses to station moves (when the feared animal moved closer), again using the enlarged +Control group. Analyses suggested that the HPA system was not completely unreactive, in that ACTH samples obtained 5 minutes after station moves (reflecting reactions to the animal being moved closer) showed significantly higher hormone levels than ACTH samples obtained when the animal had not just been moved ($t(31) = -3.62, p = .001$). The “station move” ACTH levels did not differ between the +Control and the –Control group ($t(30) = -0.06, p = .95$) and were higher than “non-move” levels for those with control ($t(20) = -3.06, p = .006$) as well as for those without experimental control over exposure pace ($t(10) = -1.95, p = .08$), although the latter was not statistically significant, likely due to the smaller sample size.

Despite the failure to find hormonal group differences as a result of our experimental manipulation of control, we did detect a significant relationship between **perceived control** and mean cortisol levels during exposure, using the entire sample to maximize power, controlling for group assignment (enlarged +Control group coded –1; –Control group coded 1) and its interaction with perceived control given that groups differed in perceived control. Our results showed that greater perceived control during exposure was significantly

associated with lower mean cortisol during exposure ($p = .003$; see Table 3, Model 1; see Figure 3). This effect was moderated by group assignment (interaction effect, $p = .002$; see Table 3, Model 1). Follow-up simple effects analyses done separately for each group (Table 3, Model 1) showed that, in the presence of actual control (+Control group), higher perceived control was strongly associated with lower mean cortisol levels during exposure. However, in the absence of actual control (– Control), subjective sense of control did not impact mean cortisol levels during exposure. Interpretation of this interaction effect is complicated because groups differed in baseline levels of perceived control (likely due to non-random composition of groups, see above, section 3.1.2).

3.2. Claustrophobia Results

Demographic, phobic severity, as well as subjective and hormonal measures for claustrophobic participants are displayed in Table 2. Claustrophobic participants with control did not differ from those without control over the exposure pace in age, $t(12) = .562$, $p = .585$, sex distribution, $X^2(1, N = 14) = 0.00$, $p = 1.00$, BMI, $t(12) = .13$, $p = .899$, aerobic exercise, $t(12) = -1.91$, $p = .081$, CGI, $t(12) = .701$, $p = .497$, CLQ, $t(12) = .620$, $p = .547$, or mean VAS fear ratings during Behavioral or Imaginative Avoidance Tests, $t(10) = -1.067$, $p = .311$, $t(11) = -.750$, $p = .469$, respectively. As expected, +Control participants had greater perceived control during exposure ($t(12) = 3.50$, $p = .004$), though differences already existed at baseline, $t(12) = 3.00$, $p = .011$. Claustrophobia participants numerically had lower perceived control during exposure than animal phobia participants, though this difference did not reach significance in this small sample ($p = .116$).

SUDs clearly increased in response to exposure (see Figure 4 left panel; time $F_{7,63} = 17.77$, $p < .001$), with no group differences (group $F_{1,9} = .044$, $p = .839$, group $\times$ time interaction $F_{7,63} = 0.49$, $p = .838$). Despite this rise in distress, **ACTH** and **cortisol declined** over time (see Figure 4 right panel; ACTH: time $F_{7,77} = 8.53$, $p < .001$; Cort: time $F_{7,77} = 15.03$, $p < .001$), with no group differences (ACTH: group $F_{1,11} = 0.220$, $p = .648$; group $\times$ time $F_{7,77} = 1.845$, $p = .09$; Cort: group $F_{1,11} = 2.43$, $p = .147$, group $\times$ time $F_{7,77} = 1.59$, $p = .150$). As with the animal phobias, and despite a trend for the intensification of the experience of lack of control, claustrophobic exposure elicited strong subjective distress without producing an HPA axis response.

4. Discussion

This study utilized a dyadic yoked design and phobia exposure paradigm to investigate fear-related distress and threat uncontrollability as independent or synergistic activators of the HPA axis. Results showed that subjective emotional distress per se did not activate the axis. Experimental manipulation of threat controllability also did not impact HPA responses, but *perceived control* during exposure was associated with lower cortisol – an effect that was moderated by actual experimental stressor control. These results challenge simplistic notions that subjectively reported emotional distress, or fear itself, activates this system.

Despite a dramatic increase in subjective emotional distress with exposure, there was no corresponding HPA axis reactivity, replicating findings of our early work (Curtis et al., 1976; 1978), and that of others (Diemer et al., 2016; Gustafsson et al., 2008; Kellner et al., 2012;

Lass-Hennemann and Michael, 2014; Siegmund et al., 2011; Van Duinen et al., 2008), using a carefully designed, laboratory-based experiment with access to blood samples and both ACTH and cortisol. These results are also mirrored in studies using other paradigms (Abelson et al., 2014; Abelson et al., 2008; Campbell and Ehlert, 2012; Cohen et al., 2000; Dickerson and Kemeny, 2004; Hjortskov et al., 2004; Shibata et al., 2016). The accumulating evidence challenges still prevailing but unsupported assumptions that fear is directly linked with cortisol release (Schwabe et al., 2010; Soravia et al., 2014). Conflicting results using exposure paradigms with anxiety disorders exist (Alpers et al., 2003; Schumacher et al., 2014). There have also been some results in healthy community samples seemingly linking the two (Al'Absi et al., 1997; Oldehinkel et al., 2011; Oswald et al., 2004; Schlotz et al., 2008), but these have been obtained using paradigms that confounded stressor uncontrollability and emotional distress. Numerous studies examined links using the Trier Social Stress Test (TSST), which is a reliable laboratory HPA axis activator but differs from our paradigm by focusing on social-evaluative threat rather than phobic fear. In TSST studies, HPA responses appear more linked to measures of threat uncontrollability than to emotional distress per se (Dickerson and Kemeny, 2004). Our phobic exposure produced a three-fold increase in subjective distress, comparable to that seen in the TSST (Hellhammer and Schubert, 2012), but our design allowed us to separately examine the effects of subjective distress and stressor uncontrollability, by experimentally manipulating control (a known HPA modulator; Dickerson and Kemeny, 2004), while matching distress levels. We produced identical results in two replications of the Curtis data (Curtis et al., 1976; 1978), using an animal fear model, and a situational fear model (claustrophobia) that allowed more ecologically realistic exposure to uncontrollable phobic cues. Overall, evidence indicated that subjective distress, at least as experienced in fear models, is not directly linked to HPA axis activation.

It must be noted here that the majority of TSST studies use “healthy” participants, whereas this study examined specific phobias. Might specific phobic participants, like those with other anxiety disorders such as panic (Petrowski et al., 2010), have biologically non-reactive HPA axes? Other data do not support this hypothesis (Plag et al., 2013) and our own data indicate that the HPA axes of our participants were indeed reactive to aspects of their experiences. First, they reacted to novelty. Both ACTH and cortisol were elevated during first laboratory experience (accommodation), relative to exposure, even though distress was much lower during accommodation. HPA reactivity to novelty, and adaptation with repeated experience, is seen in both healthy and specific phobia participants (Curtis et al., 1976; Davis et al., 1981; Peters et al., 2011). Notably, in this and other data (e.g., Curtis et al., 1976), novelty effects were more striking than HPA responses to the more emotionally distressing fear exposure. Second, specific phobia participants reacted to station moves. ACTH levels rose briefly when the feared animal was moved closer. This supports preserved HPA reactivity, perhaps to the perceived threat of approaching harm, congruent with evidence linking potential threats to one's physical or social integrity to HPA axis reactivity (Dickerson and Kemeny, 2004). It could also reflect reactivity to perceived low control (passively observing the feared animal approaching), congruent with evidence linking uncontrollable stress to HPA axis reactivity (Dickerson and Kemeny, 2004). These interpretations are speculative, since we did not measure perceived threat or low control

perceptions in response to station moves. However, the data do indicate that the HPA axes of our specific phobia participants were in fact reactive – to specific features of the stress context, perhaps related to novelty, perceived threat, and uncontrollability (Davis et al., 1981; Dickerson and Kemeny, 2004; Peters et al., 2011) – but were not linked to their emotional distress *per se*.

Our direct test of the impact of stressor uncontrollability on HPA axis reactivity produced mixed results. Our dyadic design produced well-matched groups who responded to identical exposure with similar distress, but with differing experiences of control, but, contrary to expectations, the denial of actual control over the timing of next exposure (in the –Control group) did not produce the predicted elevations in hormonal responses. On the other hand, we did find a relationship between *perceived* control and cortisol during exposure, in that greater perceived control was linked with lower cortisol. This is consistent with prior findings that perception of control is associated with smaller HPA responses to psychosocial stress (Dickerson and Kemeny, 2004; Pruessner et al., 2005; Pruessner et al., 1999). These results add to other laboratory studies that have identified control as a critical HPA axis modulator. Our data also suggest an interaction between perceptions of control and experimental manipulation of control, in that those who had actual control over the exposure pace experienced stronger cortisol buffering effects of perceived control. Though interpretation of this interaction is complicated because of baseline differences in perceived control (see below), other studies suggest that perception of control and actual control interact, often in complex ways (Agrigoroaei et al., 2013; Lundberg and Frankenhaeuser, 1978). For example, participants with greater internal locus of control showed reduced cortisol responses to a noise-cognitive paradigm (completing arithmetic tasks under noise exposure) only if they were given control over the noise intensity and actually believed that they had control over the stressor (Bollini et al., 2004). Perceived and actual aspects of stressor controllability (or lack thereof) likely interact to influence neuroendocrine responses.

There are several factors that might explain why we did not see the expected effect of direct manipulation of control on hormone levels. Unfortunately, groups differed in perceived control at baseline, with the +Control group starting out higher in perceived control and the –Control group starting out lower. The manipulation was expected to increase perceived control in the +Control group and reduce perceived control in the –Control group. We did not succeed in the latter effort (perceived control did not significantly decrease in the –Control group from before to during exposure, whereas it did significantly increase in the +Control group), perhaps because the –Control group started out with low perceived control. It might be that a sense of *loss* of control is a key variable in triggering HPA axis activation, and these participants already felt sufficiently out of control to start with that they did not experience much loss. *Loss* of control would be most directly experienced during station moves, and these did elicit HPA responses, in both groups. Further work is needed to more directly and successfully manipulate perceived loss of control to test this hypothesis – for example by initially offering control and then removing it. Replication with groups of similar baseline control perceptions would also be important.

It is also possible that our IRB imposed obligation to keep animals caged undermined our ability to more successfully reduce perceived control. The animals were never truly “uncontrolled.” We could increase perceived control (in the +Control group) by a verbal approach that emphasized their control over the timing of station moves; but imposing station moves on the –Control group when the animal was always inescapably enclosed did not reduce their sense of control. We also could not directly control an additional important variable – animal movements within the cage. Subjectively, it did appear that when the animal moved it intensified fear and the sense that the animal was not fully “under control.” However, animal movements were randomly distributed and occurred in both groups, contributing “noise” variance to our test of the control manipulation effect. This warrants further study, and animal movement should be recorded and quantified in future studies. However, we did partially address this by adding the claustrophobia study. We expected the experience of loss of control to be more directly palpable in this exposure, since participants were being moved deeper into the scanner tunnel without their specific permission in the –Control group, and though they could abort the experiment and be pulled out, that took time and was probably socially difficult, so the sense of being “stuck” was probably greater. Despite this, we still did not see a meaningful rise in cortisol, despite high distress and low perceived control. Other paradigms may be needed to further test the hypothesis that if perceived uncontrollability does impact HPA axis activity, direct manipulation of control, or loss thereof, should be able to directly alter hormonal levels in stress paradigms. An alternative hypothesis may be that trait factors that shape proclivities to feel in or out of control may also impact HPA reactivity, and may be shaping results when relationships are seen between these variables.

Our study has important limitations. The sample size was small, so replication with a larger sample is needed. It is also possible that sex moderated obtained results. Sex was equally distributed across the groups, so sex differences did not impact group comparisons, but sex differences could add variability, masking other effects; so sex effects should be examined in a study powered to detect them. However, available data do not suggest sex differences in controllability (Agrigoroaei et al., 2013) and effects of control on HPA responses have been found in both mixed (Bollini et al., 2004) and male only samples (Pruessner et al., 2005).

It is also possible that exposure to the feared stimulus in the screening BAT, which used the same stimuli and context as the 60-minute exposure, may have reduced fear during exposure and thus enhanced probability of confirming our hypothesis that the HPA axis would not respond to phobic exposure. However, BAT procedures were very brief (ranging from 30 seconds to a maximum of 3 minutes). They were unlikely to produce fear habituation, and participants in fact still reported levels of fear/distress during exposure that were as high as those seen during the BAT, confirming a lack of habituation. It is possible that prior exposure to the BAT reduced the novelty of seeing the animal in its cage or the mock MRI machine, but we wanted to minimize the known novelty effect on cortisol because we were trying to hone in on fear and control.

Another limitation is that the dyadic yoked design precluded random assignment to the two groups. This was necessary to test our primary hypothesis about the effect of control over exposure pace on the HPA response, which required us to equilibrate emotional reactivity

across the two groups. However, it also created risk of group differences in variables not considered in the matching process. Unfortunately, there were some differences suggesting that the –Control group began the study more prone to distress and to perceived low control. We do not think this undermines results and conclusions, especially since the main conclusions do not rely on group differences and because it seems extremely unlikely that we would have found a group effect of our control manipulation had we not had the bad luck of a –Control group that started out more prone to negative affect. However, the baseline differences do create some uncertainty, and replication with efforts to insure baseline as well as during exposure equivalence in emotional measures is needed. Such replication should also add psychometrically established scales to measure control perceptions (Pruessner et al., 2005; Pruessner et al., 1997) in addition to the type of VAS scales employed here.

Taken together, our data suggest that subjective emotional distress did not activate the HPA axis in this phobic fear exposure model. However, cortisol variations to fear were buffered by perceived control – an effect that was moderated by actual control over the stressor. Control expectancies probably result from repeated experiences of having or not having control over time and can, like other developmental experiences (e.g., see Heim, et al., 2000), shape adult HPA axis reactivity. In addition, current contextual factors (e.g., actual controllability, novelty, perceived support) can moderate HPA axis activity (Dickerson and Kemeny, 2004; Levine, 2000). It is likely that developmentally-shaped psychosocial “trait” factors interact with such contextual factors to influence neuroendocrine responses in humans (e.g., Cosley et al., 2010; Mayer et al., 2014) and animals (Stocker et al., 2016). This interactive model is consistent with the function of the HPA axis to appropriately respond to acute and repeated stress experiences, based on current stressor characteristics and past environmental experiences. A better understanding of psychosocial modulation of the HPA axis, and the neural pathways and mechanisms through which it occurs, both acutely and chronically, will be a critical step to illuminate its role in stress-related physical and mental illness and its potential as a treatment target to promote healthy development and adaptive resilience. Our data, together with other evidence (Abelson et al., 2008; Bollini et al., 2004; Dickerson and Kemeny, 2004), suggest that increasing control perceptions and creating opportunities to exert stressor control might be beneficial in reducing the deleterious impact of stress, at least for some people.

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Highlights

- We examined the impact of distress and control on HPA responses to phobic exposure.
- Exposure elicited intense distress without a corresponding HPA axis response.
- Our manipulation of control over the exposure of pace did not impact HPA responses.
- Perceived control during exposure, moderated by actual control, buffered cortisol.
- Our results challenge the notion that HPA axis activity reflects subjective distress.

Figure 1.

Mean $\pm$ SE Subjective Units of Distress (SUDs) in animal phobia participants increased dramatically in response to phobic fear exposure, irrespective of our experimental manipulation of control (groups with vs. without experimental control over exposure pace).

Figure 2. Mean $\pm$ SE ACTH (left panel) and plasma cortisol (right panel) in animal phobia participants declined during phobic fear exposure, irrespective of our experimental manipulation of control (groups with vs. without control over exposure pace) and despite the dramatic increase in subjective distress (see Figure 1).

Figure 3.

Greater perceived control during exposure (mean-centered) was associated with lower mean cortisol levels during exposure, controlling for group assignment (with vs. without experimental control over exposure pace) and its interaction with perceived control during exposure.

Figure 4. Mean $\pm$ SE Subjective Units of Distress (SUDs, left panel) and plasma cortisol (right panel) in claustrophobia participants. Despite the dramatic increase in subjective distress, cortisol declined during phobic fear exposure.

Mean ($\pm$ SD) for demographics, phobic severity, as well as subjective and hormonal measures in the animal phobia sample.

Table 1

	–Control (n = 11)	+ Control (n = 12)	+Control/unmatched (n = 9)	enlarged +Control (n = 21)
Demographics				
Age (years)	20.82 (2.60)	22.92 (3.32)	23.89 (7.15)	23.33 (5.17)
Sex (percent female)	45.50	41.70	55.60	47.60
Body-Mass-Index (BMI)	23.34 (2.06)	24.13 (2.95)	22.79 (3.49)	23.55 (3.18)
Aerobic Exercise (hours per week)	3.64 (3.08)	2.34 (3.59)	4.56 (3.70)	3.29 (3.72)
Alcohol Use (drinks per week)	1.42 (2.39)	1.33 (1.66)	1.11 (0.93)	1.24 (1.37)
Phobic Severity				
Phobic Animal (percent spider)	63.60	66.70	55.60	61.90
Clinical Global Impressions (CGI) Scale	6.36 (1.03)	6.50 (0.80)	6.44 (0.88)	6.48 (0.81)
Spider/Snake Phobia Questionnaire	22.36 (3.53)	21.25 (5.38)	20.11 (5.09)	20.76 (5.16)
Behavioral Avoidance Test mean VAS fear rating	52.44 (13.43)	51.88 (14.79)	46.01 (11.61)	49.36 (13.53)
Subjective Measures				
mean SUD prior to exposure (baseline)	22 (18)	12 (14)	17 (17)	14 (15)
mean SUD during exposure	49 (26)	46 (17)	49 (17)	47 (16)
peak SUD during exposure	71 (23)	70 (19)	69 (17)	70 (18)
mean SUD during accommodation *	20 (15)	4 (4)	20 (23)	10 (17)
mean VAS distress prior to exposure (baseline)	26 (22)	19 (18)	26 (22)	22 (20)
mean VAS distress during exposure	43 (19)	39 (15)	44 (17)	42 (15)
peak VAS distress during exposure	53 (23)	52 (13)	58 (23)	54 (18)
mean VAS distress during accommodation *	22 (12)	5 (5)	20 (20)	12 (15)
mean VAS perceived control prior to exposure (baseline)	49 (34)	72 (15)	68 (27)	70 (21)
mean VAS perceived control during exposure	50 (32)	83 (16)	74 (28)	79 (22)
peak VAS perceived control during exposure	55 (31)	88 (14)	78 (27)	84 (20)
mean VAS perceived control during accommodation *	50 (29)	73 (13)	61 (30)	68 (23)
Hormonal Measures				
mean ACTH prior to exposure (baseline)	21.48 (8.01)	22.68 (7.75)	20.60 (6.92)	21.79 (7.30)
mean ACTH during exposure	18.18 (5.10)	20.20 (7.73)	15.84 (5.13)	18.33 (6.95)
peak ACTH during exposure	20.41 (4.97)	21.94 (7.91)	17.82 (5.21)	20.17 (7.05)
mean ACTH during accommodation *	17.22 (7.66)	21.39 (9.77)	18.38 (6.25)	20.19 (8.48)

	-Control (n = 11)	+ Control (n = 12)	+Control/unmatched (n = 9)	enlarged +Control (n = 21)
mean cortisol prior to exposure (baseline)	10.42 (4.49)	9.10 (2.85)	11.31 (6.51)	10.05 (4.76)
mean cortisol during exposure	8.06 (2.12)	7.02 (2.04)	10.18 (5.74)	8.37 (4.25)
peak cortisol during exposure	9.55 (2.74)	8.21 (2.46)	12.11 (7.22)	9.88 (5.30)
mean cortisol during accommodation *	8.35 (2.93)	8.53 (2.81)	12.31 (9.05)	10.15 (6.39)

Note: SUD = Subjective Units of Distress; VAS = Visual Analog Scales

* Averaging over accommodation time points that corresponded to the measurement time points during phobic exposure

Table 2

Mean ($\pm$ SD) for demographics, phobic severity, as well as subjective and hormonal measures in the claustrophobia sample.

		–Control (n = 7)	+ Control (n = 7)
Demographics	Age (years)	21.57 (4.12)	23.00 (5.32)
	Sex (percent female)	42.90	42.90
	Body-Mass-Index (BMI)	25.29 (0.98)	25.44 (3.04)
	Aerobic Exercise (hours per week)	7.00 (3.37)	2.61 (5.09)
Phobic Severity	Clinical Global Impressions (CGI) Scale	6.00 (1.00)	6.43 (1.27)
	Claustrophobia Questionnaire	52.86 (11.28)	57.14 (14.42)
	Behavioral Avoidance Test mean VAS fear rating	65.56 (13.58)	56.97 (14.27)
	Imaginative Avoidance Test mean VAS fear rating	62.60 (15.06)	55.81 (17.60)
Subjective Measures	mean SUD prior to exposure (baseline)	12 (12)	9 (12)
	mean SUD during exposure	35 (18)	41 (20)
	peak SUD during exposure	65 (21)	72 (21)
	mean SUD during accommodation *	9 (7)	7 (8)
	mean VAS distress prior to exposure (baseline)	26 (31)	25 (15)
	mean VAS distress during exposure	26 (10)	35 (18)
	peak VAS distress during exposure	36 (19)	40 (20)
	mean VAS distress during accommodation *	6 (6)	15 (16)
	mean VAS perceived control prior to exposure (baseline)	42 (17)	72 (20)
	mean VAS perceived control during exposure	41 (12)	72 (20)
	peak VAS perceived control during exposure	49 (18)	75 (17)
	mean VAS perceived control during accommodation *	45 (23)	77 (16)
Hormonal Measures	mean ACTH prior to exposure (baseline)	20.67 (10.22)	16.11 (5.53)
	mean ACTH during exposure	12.76 (2.94)	12.06 (4.52)
	peak ACTH during exposure	14.09 (2.94)	13.73 (4.73)
	mean ACTH during accommodation *	16.79 (5.95)	14.74 (5.94)
	mean cortisol prior to exposure (baseline)	9.50 (2.78)	6.40 (2.40)
	mean cortisol during exposure	6.03 (2.11)	4.57 (1.99)
	peak cortisol during exposure	7.05 (2.12)	5.35 (2.35)
	mean cortisol during accommodation *	5.90 (1.93)	5.31 (1.12)

Note: SUD = Subjective Units of Distress; VAS = Visual Analog Scales

* Averaging over accommodation time points that corresponded to the measurement time points during exposure

Table 3

Linear multiple regression on mean hormonal concentrations during exposure as a function of perceived control during exposure, experimentally manipulated control, and their interaction.

Dependent variable	Sample	R ²	Predictor variable	β	SE	t	p
Model 1 Cortisol ^a	All participants	0.43	Perceived control	-0.07	0.02	-3.26	0.003
			Experimentally manipulated control	-0.81	0.62	-1.31	0.200
	Participants with experimental control	0.48	Interaction of perceived-by-manipulated control	0.07	0.02	3.33	0.002
	Participants without experimental control		Perceived control	-0.14	0.03	-4.20	<.001
Model 2 ACTH ^a	All participants	0.09	Perceived control	0.001	0.02	0.06	0.952
			Experimentally manipulated control	0.06	0.05	1.37	0.182
	Participants with experimental control	0.12	Interaction of perceived-by-manipulated control	0.59	1.35	0.44	0.664
	Participants without experimental control		Perceived control	-0.05	0.05	-1.06	0.296
Model 3 ACTH station move ^b	All participants	0.07	Perceived control	0.11	0.07	1.59	0.129
			Experimentally manipulated control	0.01	0.05	0.26	0.802
	Participants with experimental control	0.08	Interaction of perceived-by-manipulated control	0.07	0.05	1.26	0.219
	Participants without experimental control		Perceived control	0.85	1.60	0.53	0.598
Model 4 ACTH station move ^b	All participants	0.03	Perceived control	-0.04	0.05	-0.80	0.432
			Experimentally manipulated control	0.11	0.09	1.26	0.223
	Participants with experimental control	0.03	Interaction of perceived-by-manipulated control	0.02	0.05	0.52	0.618
	Participants without experimental control		Perceived control	0.02	0.05	0.52	0.618

Note:

^aMean hormonal concentrations during exposure.

^bMean ACTH levels in response to station moves.