Phobic fear does not activate the HPA axis – yet the system is responsive.

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Brief Abstract

Specific phobia subjects failed to show HPA responses to phobic exposures, despite intense distress. However, the system was still responsive, showing ACTH pulses when the phobic object was moved closer. This indicates that in specific phobias, the HPA axis remains reactive to aspects of the stress context but does not respond in concert with fearful distress itself. In addition, trait perception of control shaped HPA responses in interaction with the context (our control manipulation). These results call for a more nuanced approach of what is truly "stressful" to the human HPA axis system.

Methods

Sample:

- All participants (n = 32; 18-45 years old) were diagnosed with a specific phobia of spiders or snakes with no current psychiatric comorbidity (as determined by DSM-IV criteria and SCID interview).

Procedure and experimental manipulation:

- Participants underwent exposure therapy in which they were gradually exposed to their feared animal (live animal in aquarium) over a series of 6 specified stations.
- The starting station (#1) was outside the testing room and the closest station (#6) was immediately in front of participants with their hands on the glass aquarium.
- We examined HPA responses when the pace of exposure was clearly placed under the control of the subject ("**control**") compared to when an identical exposure was given to a matched phobic participant in the absence of control ("**yoked**").

Sampling procedure:

- Participants reported to the laboratory at 1:00 p.m. and IV was inserted at 1:30 p.m. followed by a 1 hour accommodation period.
- Baseline blood samples were obtained at 2:00 p.m. (minus 30 min) and at 2:25 p.m. (minus 5 min). Exposure began around 2:30 p.m. and continued for 60 minutes, with scheduled blood sampling at 15, 30, 45, 60, 75 and 90 minutes after initiation.
- Additional samples for ACTH were obtained 5 min after each time the animal was moved one step closer (ACTH levels in response to station moves).

Outcome variables

- Plasma ACTH and cortisol levels
- Subjective responses (distress, perceived sense of control) were also quantified on 100 mm Visual Analogue Scale (VAS) lines.

References:

Curtis, G. C., Nesse, R., Buxton, M., & Lippman, D. (1978). Anxiety and plasma cortisol at the crest of the circadian cycle: Reappraisal of a classical hypothesis. *Psychosomatic Medicine*, *40*(5), 368-378.

Dickerson, S. S., & Kemeny, M. E. (2004). Acute stressors and cortisol responses: A theoretical Integration and synthesis of laboratory research. *Psychological Bulletin*, *130*(3), 355-391.

Levine, S. (2000). Influence of psychological variables on the activity of the hypothalamic–pituitary–adrenal axis. *European Journal of Pharmacology*, *405*(1), 149-160.

Introduction

- Hypothalamic-pituitary adrenal (HPA) dysregulation is associated with a wide range of psychiatric disorders, but mechanisms remain unclear.
- Clarifying mechanisms requires understanding of psycho-biological linkages:
  There has long been an implicit assumption that intense *subjective distress* (e.g., fear) should activate the HPA axis.
  - This assumption was challenged 25 years ago (Curtis et al., 1978), but laboratory studies in humans are limited and it is possible that HPA reactivity is generally suppressed in people with long standing phobias.
  - In this study we sought to replicate Curtis` findings that intense fearful distress does not trigger HPA axis activity.
- Instead, animal models show that contextual factors such as novelty, control, predictability and social buffering are particularly salient to HPA axis activity (Levine, 2000).
- Such factors have only rarely been directly examined in human studies, but a theoretically driven meta-analysis (Dickerson & Kemeny, 2004) highlights the importance of stressor controllability and social context in modulating HPA activity.
- In this study we used a phobic exposure model to test whether level of *control* over an aversive stressor shapes stress reactivity even if intense fear does not.

Discussion

- These data replicate a seminal study by Curtis and colleagues (1978), showing that the intense subjective distress of phobic fear does not by itself drive HPA axis reactivity.
- Yet, the HPA system was not completely unresponsive to the subjects` experience:
  - Significant ACTH pulses occurring when the feared animal was brought closer indicate that the system was indeed "reactive," so specific phobics do not appear to be characterized by a general blunting of HPA reactivity.
  - Despite their ability to respond, we did not detect reactivity associated with fearful distress itself, supporting the hypothesis that subjectively experienced fear, even when intense, does not activate the HPA axis.
- Our direct manipulation of actual control over pace of exposure failed to modulate cortisol responses. However, preliminary analyses revealed that individual differences in subjective sense of control, even when measured at rest (suggesting a trait phenomenon), did modulate baseline cortisol levels and interacted with context (control vs. no control) in shaping mean cortisol levels during exposure.
  - In the absence of actual control, trait differences in sense of control did not impact HPA responses.
  - In the presence of actual control, a tendency to feel in control even at rest appeared to "matter" to the HPA axis, leading to reduced cortisol levels during exposure.
- Clearly, HPA axis activity does not reflect levels of subjectively reported distress. Instead, our findings suggest that subtle aspects of the stress context shape HPA axis reactivity, perhaps in interaction with trait phenomena that shape intrinsic sense of control. A psychologically nuanced approach to understanding what truly is "stressful" to the human HPA axis is needed.

Results

- **Subjective distress** increased dramatically in response to exposure (see Figure 1; time $F_{6,180}$=22.08, p < .001), with no group differences (control vs. no control) in distress levels (group $F_{1,30}$=0.35, p = .56; group × time interaction $F_{6,180}$=0.88, p = .51). Indeed, subjective distress nearly doubled from 5 minutes before to during exposure (M±SD=66±59, M±SD=126±49, t(31)=-5.50, p < .001).
- Despite this dramatic increase in distress, **cortisol and ACTH** significantly declined over time (see Figure 2; Cort: time $F_{7,210}$=12.13, p < .001; ACTH: time $F_{7,210}$=6.15, p < .001), with no group differences in hormonal levels (Cort: group $F_{1,30}$<0.001, p = .99; group × time interaction $F_{7,210}$=0.47, p = .86; ACTH: group $F_{1,30}$<0.001, p = .99; group × time interaction $F_{7,210}$=0.30, p = .95).
- We could not detect any relationships between any measures of subjective distress changes and change in ACTH or cortisol levels (all ps > .20).
- **However, the system was not unreactive** (see Figure 3): ACTH levels were quantitatively higher when the animal was first visible, though not significantly so – t(31)=-1.62, p = .12. However, ACTH levels in response to station moves were significantly greater than ACTH levels during regularly scheduled sampling, t(31)=-3.62, p = .001.
- Though direct manipulation of control (in"control" vs "yoked" comparisons) did not impact subjective or hormonal responses, regression analyses did reveal an effect of subjective **sense of control** on baseline cortisol (Figure 3 left panel; b=-.08, t(27)=-2.56, p = .02) and mean cortisol levels during exposure (b=-.07, t(27)=-3.26, p = .003). Furthermore, there was a significant interaction of perceived control and the control manipulation in shaping cortisol responses during exposure (b=.07, t(27)=3.33, p = .002). Higher perceived control was strongly associated with lower cortisol levels when subjects had actual control over the threat (see Figure 3 right panel).

FIGURE 1. Subjective distress increased dramatically in response to exposure, irrespective of our control manipulation.

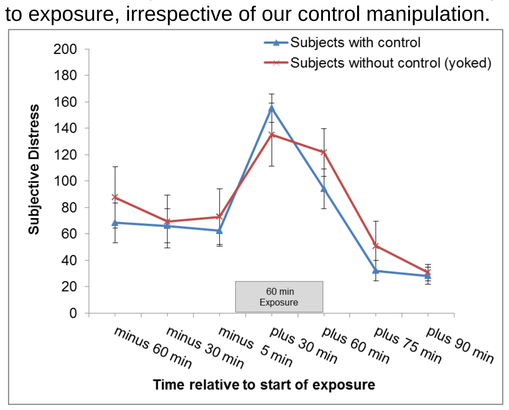
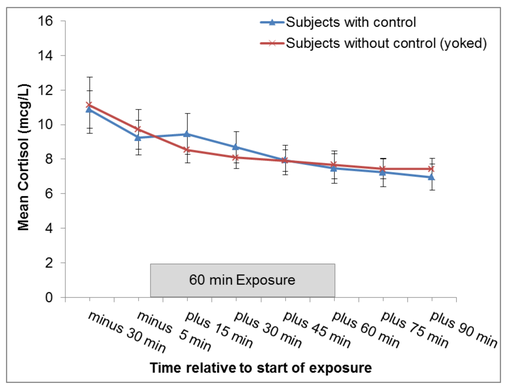


FIGURE 2. Plasma cortisol (left panel) and ACTH (right panel; mean±SE) levels declined in response to exposure, irrespective of our control manipulation and despite the dramatic increase in subjective distress (see Figure 1).



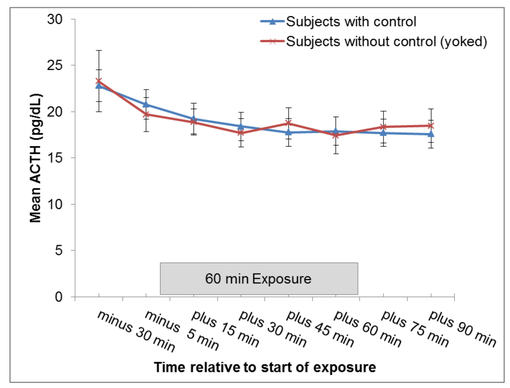
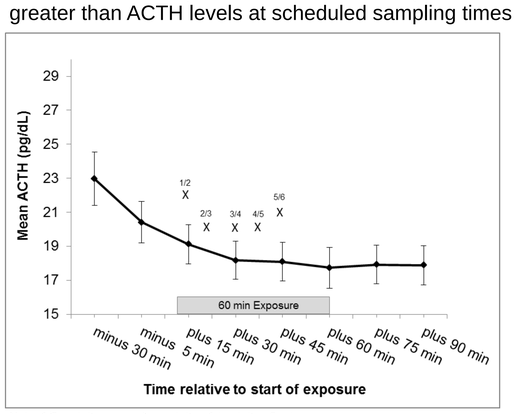
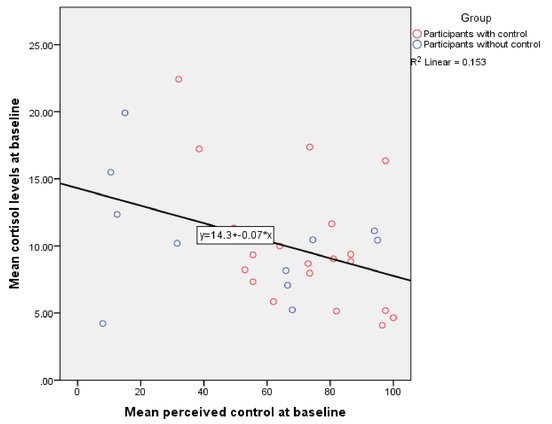


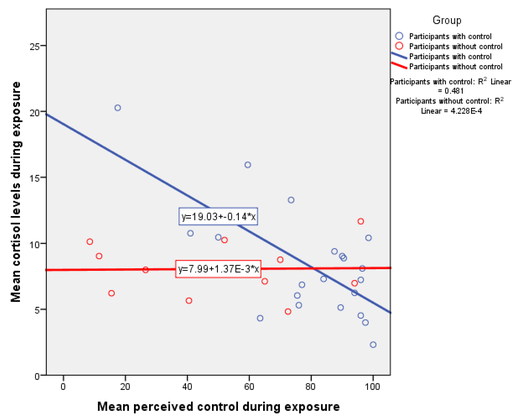
FIGURE 3. ACTH pulses to station moves (indicated by X) were greater than ACTH levels at scheduled sampling times (solid line).



Note: 1/2 = station move from station 1 to station 2, etc.

FIGURE 4. Individual differences in "trait" perception of control reduced baseline cortisol (left panel) and reduced mean cortisol levels during exposure only when subjects had actual control over the exposure (right panel).





No disclosures