HUMAN PSYCHOPHARMACOLOGY
Hum Psychopharmacol Clin Exp 2006; **21**: 377–385.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/hup.778

Stress reactivity: biological and subjective responses to the cold pressor and Trier Social stressors†

Aimee L. McRae[1]*, Michael E. Saladin[2], Kathleen T. Brady[1], Himanshu Upadhyaya[1], Sudie E. Back[1] and Mary Ann Timmerman[3]

[1]*Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, South Carolina, USA*
[2]*College of Health Professions, Medical University of South Carolina, Charleston, South Carolina, USA*
[3]*Department of Biometry and Epidemiology, Medical University of South Carolina, Charleston, South Carolina, USA*

The cold pressor test (CPT) and Trier Social Stress Test (TSST) have been shown to reliably increase HPA activity; however, little research has compared responses to these stressors. In this study, biological (plasma cortisol and ACTH levels) and subjective (e.g., stress and mood) responses were compared in 31 subjects administered both the CPT and TSST. Subjects were diagnosed with alcohol dependence and post-traumatic stress disorder (PTSD) ($n = 11$), alcohol dependence without PTSD ($n = 10$), PTSD without alcohol use disorder ($n = 4$), and neither PTSD nor alcohol use disorder ($n = 6$). All subjects completed both the CPT and TSST. In all groups, the TSST elicited higher levels of ACTH and cortisol than the CPT, and the response time course differed between tasks. The TSST also produced lower mood ratings than the CPT. A comparison of all diagnosed groups with normal controls revealed group differences in ACTH responding for the CPT but not the TSST. The results suggest that the TSST results in a greater HPA response than the CPT; however, the CPT may have utility in diagnostically heterogeneous patients.

KEY WORDS — HPA axis; stress; ACTH; cortisol; alcohol; PTSD

INTRODUCTION

Endocrine and subjective responses to physical and psychological stressors have been well described (Murberg, 1994; Friedman *et al*., 1995). These stressors are commonly used to stimulate the hypothalamic-pituitary-adrenal (HPA) axis, one of the main hormonal systems involved in the stress response. Challenging the HPA axis with stressors has been instrumental in assessing the neurobiology of individuals with psychiatric or medical disorders.

Two of the most commonly used stress tasks are the cold pressor test (CPT) and the Trier Social Stress Test (TSST). The CPT consists of submerging the hand up to the wrist in cold water (0–4°C) for 1 or 2 min. This test has been shown to reliably increase sympathetic nervous system and HPA axis activity by activation of thermal and nociceptor afferents (Bullinger *et al*., 1984; Edelson and Robertson, 1986; Velasco *et al*., 1997; Kelly and Cooper, 1998) and has been previously used to elicit a stress response and activate the HPA system (Errico *et al*., 1993; Pascualy *et al*., 2000).

The TSST involves an anticipation period and delivery of a speech and performance of a mental arithmetic challenge in the presence of an audience. This task has been shown to induce considerable changes in neuroendocrine parameters, including concentrations of adrenocorticotropin hormone (ACTH), cortisol, growth hormone, and prolactin (Kirschbaum *et al*., 1993).

* Correspondence to: A. L. McRae, Clinical Neuroscience Division, Medical University of South Carolina, 67 President Street, Charleston, SC 29425, USA. Tel.: (843) 792-5205. Fax: (843) 792-4817. E-mail: mcraeal@musc.edu
†Aimee L. McRae, Himanshu Upadhyaya, Sudie E. Back are Assistant Professors; Michael E. Saladin is a Associate Professor; Kathleen T. Brady is a Professor; Mary Ann Timmerman is a Doctoral candidate.

Contract/grant sponsor: NIAAA; contract/grant number: #2P50AA10761.
Contract/grant sponsor: General Clinical Research Center USPHS; contract/grant number: #M01RR01070.

Received 25 January 2006
Accepted 17 May 2006

Although both the CPT and TSST have been shown to reliably increase HPA activity, to our knowledge no comparison of responses to these stressors has been previously published. Such a comparison could potentially demonstrate the relative effectiveness of these paradigms in eliciting a stress response. This preliminary report is part of a larger study of stress responding in individuals with PTSD, alcoholism, or both. In a subset of subjects, both the TSST and CPT were administered. In this report, biological (plasma cortisol and ACTH levels) and subjective (e.g., stress and mood, nervousness) responses in subjects who participated in both the CPT and TSST are compared.

MATERIALS AND METHODS

Subjects

The sample consisted of 31 participants (17 males/14 females). The mean age of the sample was 30.7 years (±8.6) with: 80.6% Caucasian ($n = 25$), 16.1% African American ($n = 5$), and 3.2% other ($n = 1$). Approximately half of the participants were cigarette smokers (46.7%, $n = 14$).

Subjects were recruited primarily via media advertisements over a 36-month period. Subjects were participating in a larger non-treatment study examining stress activity in individuals with alcohol dependence and post-traumatic stress disorder (PTSD) (35%, $n = 11$), alcohol dependence only (32%, $n = 10$), PTSD only (14%, $n = 4$), and neither disorder (19%, $n = 6$). The percentage of the sample with any other axis I disorder was 45.2 ($n = 14$). Eleven subjects met criteria for an anxiety disorder (social phobia, $n = 5$; generalized anxiety disorder, $n = 3$; panic disorder, $n = 2$; specific phobia, $n = 1$); four subjects reported past depressive episodes or disorder; five subjects met criteria for dysthymia; and seven subjects met criteria for past substance dependence or current substance abuse.

Written informed consent was obtained before study assessments were administered. All study procedures and consent forms were approved by the Medical University of South Carolina's Institutional Review Board.

Individuals meeting study criteria were subsequently scheduled for a history and physical examination and two laboratory sessions. General exclusion criteria included (1) current major depressive disorder; (2) history of or current medical conditions that might interfere with safe conduct of the study or affect HPA activity; (3) history of or current psychotic, eating, or bipolar affective disorders; (4) synthetic glucocorticoid or exogenous steroid therapy within one month of testing; (5) pregnancy, nursing, or ineffective means of birth control; (6) receiving opiates within 2 weeks of testing; (7) currently receiving naltrexone or a known sensitivity to naltrexone; or (8) DSM-IV criteria for substance dependence except alcohol or nicotine within the past 60 days.

Methods

Assessments. Patients meeting preliminary screening criteria were evaluated for study eligibility with the SCID-IV, which permits accurate diagnosis of lifetime and current psychiatric disorders using DSM-IV criteria (First *et al*., 1994). The Clinician Administered PTSD Scale was used to assess symptoms of PTSD (Blake *et al*., 1995).

All subjects were required to abstain from alcohol for a minimum of 5 days prior to testing. Abstinence was assessed via self-report and breathalyzer readings. This abstinence period was required as HPA axis function can be profoundly affected by alcohol withdrawal as evidenced by an increase in both ACTH and cortisol for several days after last alcohol use in alcohol-dependent subjects (Adinoff *et al*., 1990). However, many of these changes, specifically the increase in basal circulating cortisol and ACTH, may normalize after the acute withdrawal period (Heinz *et al*., 1995). The two laboratory sessions were conducted at the General Clinical Research Center (GCRC) of the Medical University of South Carolina.

Stress reactivity procedures

Cold pressor session. Subjects were admitted to the GCRC the evening prior to testing. Subjects dependent on nicotine were provided with a nicotine patch on admission. Subjects were awakened at 0600 h the morning of the test session and an IV catheter was placed in the anticubital area of the non-dominant arm. They received a standard breakfast at 0700 h and were subsequently seated in a comfortable chair for a 30-min acclimation period and to complete pre-task subjective scales. Pre-session subjective scales included the Craving/Distress/Mood Scale, a modification of the Within Session Rating Scale designed to rapidly assess craving and other mood feeling states (including stress) during the test session (Childress *et al*., 1986). This 100-mm visual 10-point Likert scale is anchored with adjectival modifiers (''not at all'' to ''extremely''). This scale was also utilized at each of the five post-task assessment time points.

After the acclimation period, two baseline assessments of neuroendocrine parameters were obtained 10-min apart to provide for a more stable index for

challenge response comparisons. The CPT was administered in a manner consistent with its previous use with non-clinical populations (Blandini *et al*., 1995; Peters *et al*., 1998). Briefly, subjects were asked to submerge one hand in an ice water bath up to the wrist for as long as they could or a maximum of 1 min.

Immediately following the CPT, subjective ratings were obtained, and blood was collected for neuroendocrine measures (ACTH and cortisol). Neuroendocrine samples and subjective ratings were further assessed at 5-, 30-, 60-, and 120-min intervals post-task. Blood samples were collected in EDTA-prepared tubes and immediately placed on ice. Plasma was obtained by centrifugation under refrigeration and the serum sample frozen at −70°C until assayed in duplicate. Allegro HS-ACTH system (Nichols Institute Diagnostics), which has an intra-assay c.r. of 6% with a sensitivity of 1 pg/ml, was used for ACTH assays. Cortisol was assayed using the Roche Diagnostic Elecsys 2010 immunoassay analyzer and kits based on an electrochemiluminescence competitive immunoassay having a functional sensitivity of 8.0 mmol/L (0.29 μg/dl) and intra-assay reproducibility of less than 2%. GCRC personnel collected all samples. Subjects were debriefed and paid for their participation prior to discharge.

Trier session. Thirty-one subjects who completed the CPT also completed the TSST. The admission for the TSST was generally within 2 months after completion of the CPT. The process for admission was identical to that described above. At 0800 h, subjects were told they were going to be asked to give an impromptu speech describing their qualifications for a job and they were given 10 min to prepare the speech. Three individuals not previously known to the subjects entered the room and the subject was instructed to speak for 5 min. Following the speech, the subject was asked to perform a 5-min math challenge exercise, specifically, counting backwards from 1022 by 13 as quickly and accurately as possible. If an error was made, the subject was instructed to begin again at 1022. Neuroendocrine and subjective measures were obtained as described for the CPT. The subject was debriefed and compensated prior to discharge.

Statistics. The primary dependent measures were plasma ACTH and cortisol levels, subjective stress and mood. The primary data analytic procedure used in this study was the repeated measures ANOVA. Additionally, paired and independent sample *t*-tests were used where appropriate. To determine between-stressor concordance of response, Pearson product moment correlations were used. Six correlations were performed for each measure, with each correlation involving a measurement obtained during the CPT and the corresponding measure (and time point) obtained during the TSST. All correlations were performed on deviation scores, where the participant's baseline response was subtracted from their response at each of the other assessment time points. A Bonferroni correction was applied to control for the inflated alpha resulting from multiple correlations.

RESULTS

Comparison of CPT vs. TSST on measures of neuroendocrine and subjective reactivity

Neurobiological reactivity. Paired *t*-tests indicated that the two ACTH and cortisol baseline values obtained prior to the CPT were not statistically different and therefore were averaged (ACTH, baseline 1 = 25.5 pg/ml, baseline 2 = 26.6 pg/ml; cortisol, baseline 1 = 17.0 μg/dl, baseline 2 = 17.2 μg/dl). Also, the two baseline values obtained prior to the TSST were not statistically different and were averaged (ACTH, baseline 1 = 21.6 pg/ml, baseline 2 = 22.9 pg/ml; cortisol, baseline 1 = 15.4 μg/dl, baseline 2 = 15.1 μg/dl). The mean of the two baselines for each measure was then compared between tasks and again found not to be statistically different (see Fig. 1: ACTH, CPT baseline: 26.1 pg/ml, TSST baseline: 22.2 pg/ml; cortisol, CPT baseline: 17.1 μg/dl, TSST baseline: 15.2 μg/dl). The absence of statistical differences among baseline means for the CPT versus Trier stressors suggests that participants had equivalent ACTH and cortisol levels prior to each stressor. Accordingly, baseline values were not included in the subsequent analyses.

Figure 1 depicts ACTH (left) and cortisol (right) levels for baseline and for the five time periods following exposure to the CPT and TSST. As can be seen, the maximum ACTH and cortisol levels following completion of the TSST were significantly higher than following completion of the CPT. However, there were no differences between the TSST and CPT at the 120-min time point. Repeated measures ANOVAs identified significant stressor × assessment period interactions for both ACTH and cortisol, F's $(4,120) = 5.5$ and 13.1, p's <0.01, respectively. Additionally, orthogonal components for trend revealed a significant linear trend component for the cortisol interaction, F $(1,30) = 17.9$, $p = 0.001$, and significant linear and quadratic trend components for the ACTH interaction, F's $(1,30) = 6.9$ and 8.1,

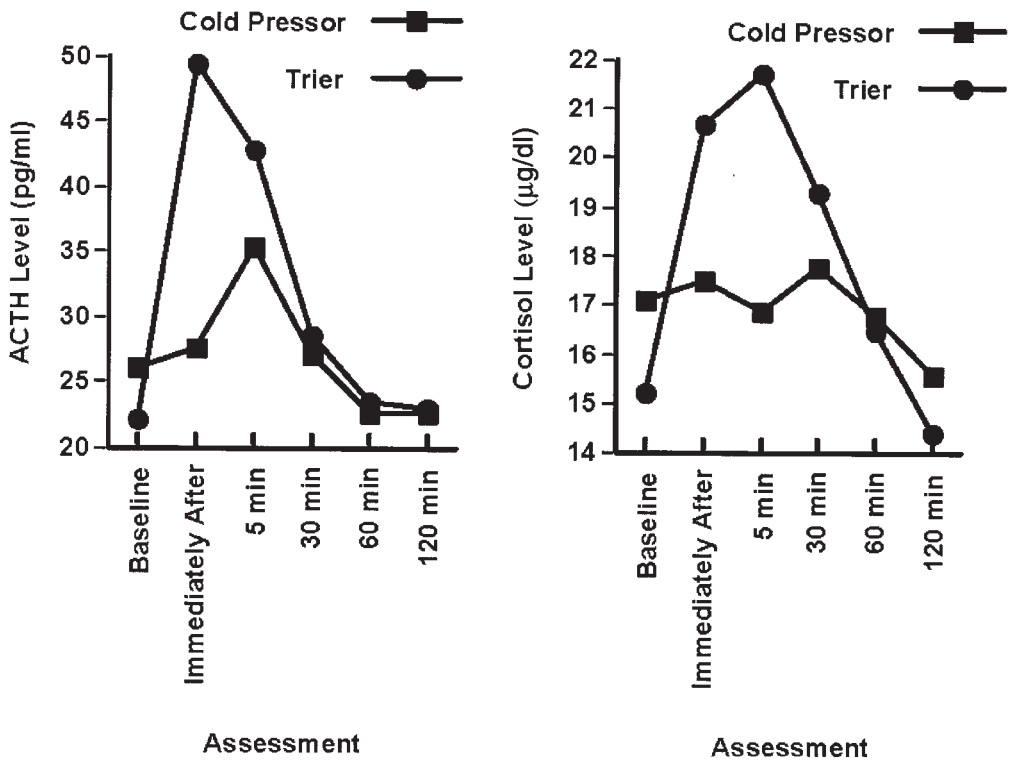

Figure 1. ACTH and cortisol levels (as a function of measurement time point)

p's ≤ 0.05. The interactions and associated linear trend components verify, as indicated in Figure 1, that cortisol and ACTH levels after the TSST were higher than for the CPT following the completion of the task and then decreased over the course of the measurement period to arrive at common endpoint values. For the TSST, the quadratic trend component for the ACTH levels verifies that stable and comparatively low levels were attained at the last two measurement time points. This was not consistent with the cortisol response to the CPT and TSST. In summary, the TSST elicited higher levels of ACTH and cortisol than the CPT and the time course of response differed. For the CPT, both ACTH and cortisol returned to baseline at the 60- and 120-min assessment points. For the TSST, there was a notable divergence in the time course for the decline in cortisol and ACTH levels, with ACTH levels reaching stable low values by the 60-min assessment point while the cortisol levels continued to decline throughout the measurement period.

Subjective reactivity. The mean baseline stress ratings for the CPT and TSST were 2.2 and 2.0, respectively. Paired t-tests failed to identify any baseline differences, $t(30) < 1.0$, $p = 0.8$. Given the apparent statistical equivalence, baseline values were excluded from subsequent analyses.

Figure 2 depicts mean stress ratings obtained during baseline and at each measurement point after the completion of the CPT and TSST. Both tasks produced high levels of stress over time and stress ratings, regardless of task, decreased across measurement time points to a common terminal level. However, subjective stress declined more slowly following the TSST than the CPT, $F\ (4,112) = 3.8$, $p < 0.01$.

Subjective mood ratings were also obtained before and after the stress tasks. Comparison of the between-task mean baseline mood ratings (5.3 vs. 4.8) found the mean for the TSST to be significantly lower than the CPT, $t(30) = 2.1$, $p < 0.05$. This finding suggests a significant anticipatory decline in mood prior to the TSST relative to the CPT.

Since baseline mood ratings were different between tasks, these baseline means were included in the analysis of the post-stressor mood ratings. Mood ratings were consistently lower prior to and following

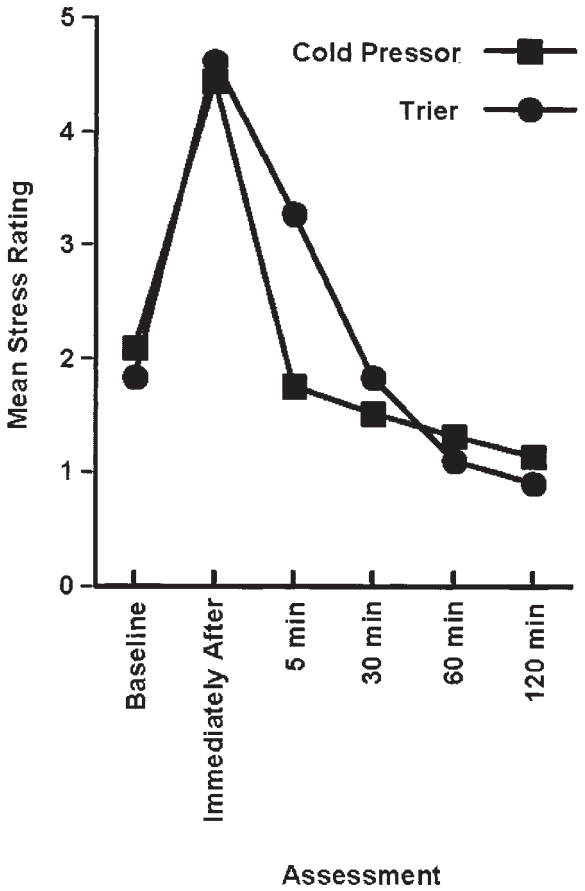

Figure 2. Mean stress rating at baseline and the five assessment time points for all groups

the TSST stressor as compared to the CPT, but both tasks yielded a common terminal mean mood rating (120-min assessment). The apparent task difference in mood ratings across the first five assessment periods was verified by a significant task main effect, $F(1,27) = 4.8$, $p < 0.05$. Thus, not only does the TSST appear to produce an anticipatory depression in mood relative to the CPT, it also appears to maintain this effect for at least an hour after stressor exposure is complete.

Diagnostic group differences in responses by task

A priori grouping factor. A series of group (4) × assessment period (6) repeated measures ANOVAs performed to determine whether there were differences by diagnostic group for any of the primary dependent measures failed to reveal either a significant interaction or main effect by group. The failure to identify group differences was probably because of the small number of individuals in each diagnostic group.

A posteriori grouping factor. A considerable body of evidence indicates that individuals with alcohol dependence, PTSD, or both disorders are likely to evidence a pattern of stress responding that is substantially different from what is observed in healthy individuals (Yehuda *et al*., 1990, 1995; Resnick *et al*., 1995; Bernardy *et al*., 1996; Costa *et al*., 1996). Given this and the small sample size of each of the a priori defined groups, comparisons of individuals with any diagnosis (alcohol dependence, PTSD, or both diagnoses; $n = 25$) to healthy controls ($n = 6$) were conducted.

Neurobiological reactivity. Figure 3 depicts the mean ACTH and cortisol levels across six assessment time points for individuals with either or both diagnoses

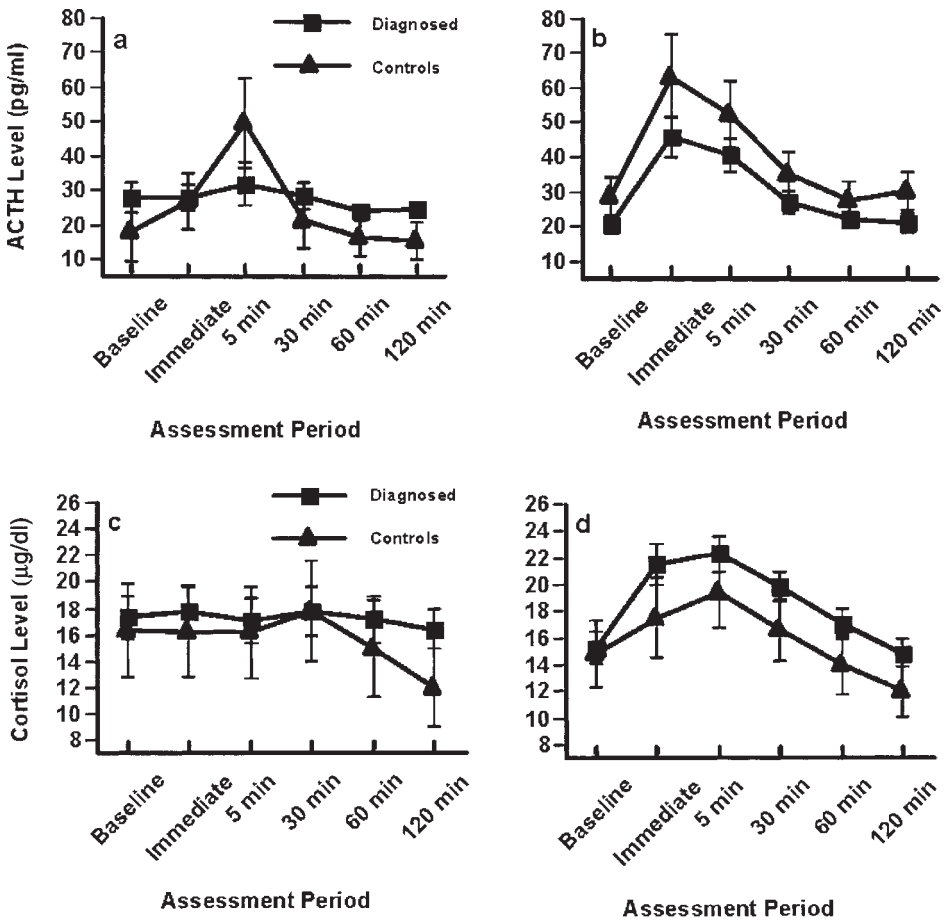

Figure 3. Mean ACTH (panels A and B) and cortisol (panels C and D) levels at baseline and at the five assessment time points following completion of the CPT (panels A and C) and TSST (panels B and D)

(Diagnosed) versus healthy controls (Controls). Paired *t*-tests applied to the mean baseline ACTH and cortisol levels failed to reveal any significant group differences. Thus, the groups evidenced similar baseline levels of plasma ACTH and cortisol prior to stressor administration.

Repeated measures ANOVAs applied to the mean ACTH and cortisol across assessment time periods (as depicted in each panel of Fig. 3) revealed a significant group (2) × assessment period (6) interaction for ACTH responding during the CPT. As can be seen in Figure 3, there is a steep rise in plasma ACTH in the Control group relative to the Diagnosed group. In sum, cortisol responding was similar across groups and stressor tasks while ACTH responding was blunted during the CPT but not the TSST in participants with alcohol dependence, PTSD, or both relative to the controls.

Subjective reactivity. Paired *t*-tests were applied to the baseline stress ratings for the CPT (Diagnosed = 2.6, Controls = 0.3) and for the TSST (Diagnosed = 2.4, Controls = 0.7). A group difference was identified for the CPT, $t(29) = 4.3$, $p < 0.001$, but not the TSST, $t(29) = 1.5$, $p = 0.14$, indicating that the diagnosed group reported greater stress prior to the CPT than Controls. There were no between-group differences in baseline mood ratings.

Repeated measures ANOVAs were applied to the group mean stress and mood ratings across assessment time points. There was a significant group main effect for the TSST mood ratings (F (1,28) = 4.6, $p < 0.05$)

indicating that the Diagnosed group reported a more negative mood following stressor exposure as compared to the Control group. The analyses failed to identify any main effect or interaction for the stress measure.

Between-stressor concordance of reactivity

Pearson correlations were performed to evaluate the extent to which individuals who responded during the CPT were also responders on the TSST. The findings are summarized in Table 1. There were significant correlations for the 60- and 120-min time points on the cortisol measure, r's 0.57 and 0.51, respectively, all p's ≤ 0.003. For mood, decreasing ratings during the CPT were associated with decreasing ratings during the TSST (all p's ≤ 0.001, see Table 1). In sum, there is minimal response concordance between the CPT and TSST for ACTH and subjective stress but considerable response concordance for subjective mood and, to a lesser extent, cortisol.

DISCUSSION

In this study, biological and subjective responses to the CPT and TSST were compared. This is the first study to our knowledge to directly compare these two stress manipulations in the same individuals. The findings suggest that a social stressor, such as the TSST, may result in an overall greater activation of the HPA axis when compared to a physical stressor such as the CPT. These differences in HPA response may be reflective of the activation of different stress pathways. Animal data suggest that limbic stress pathways are most sensitive to emotional stressors, and that following these stressors multimodal stimuli are responsible for HPA activation (Herman and Cullinan, 1997). In contrast, the limbic area of the brain does not appear to be involved in HPA response to physiological stressors. Instead, physical stressors can be relayed directly to the paraventricular nucleus by visceral efferent pathways. A recent meta-analysis found that the combination of public speaking/cognitive tasks was associated with greater cortisol response than other psychological tasks or noise exposure; however, studies involving the CPT were not included in this review (Dickerson and Kemeny, 2004).

Although a more robust response is seen with the TSST, the CPT may be a more useful tool for characterizing differential response patterns between individuals with psychiatric diagnoses and control subjects. Both alcohol dependence and PTSD are associated with characteristic alterations in the HPA axis and stress response. In particular, for both disorders, studies have indicated that there is a diminution of the stress response that may make it more difficult to find between task differences (Errico *et al*., 1993; Resnick *et al*., 1995; Ehrenreich *et al*., 1997; Vescovi *et al*., 1997; Lovallo *et al*., 2000). It would be ideal to compare the response of each diagnostic group independently to determine whether this relationship is impacted by psychiatric diagnosis. Unfortunately, the number of subjects involved in this preliminary exploration was insufficient to make statistical comparisons between the diagnostic groups. However, a comparison of all diagnosed groups with controls revealed that the CPT elicited differences in ACTH response not seen with the TSST. The lack of concordance between the CPT and TSST in neurobiologic and subjective response (with the exception of mood) also suggests a differential responding to psychological versus physical stress tasks.

The length of stressor exposure is an important consideration in this comparison. While the CPT is completed in 1 min, the TSST involves a 10-min anticipation period, a 5-min speech and a 5-min mental arithmetic test. As such, it may be that the difference in magnitude of response is related primarily to the duration of the stressor rather than the type of stressor. This difference in stressor duration

Table 1. Correlations between each dependent measure obtained during (at each assessment time point) the CPT and the corresponding measure (and time point) obtained during the TSST

	Assessment time point					
Measure	Baseline	Immediate	5 min	30 min	60 min	120 min
ACTH	0.10, $p = 0.58$	0.17, $p = 0.35$	0.23, $p = 0.23$	0.32, $p = 0.09$	0.29 $p = 0.12$	0.29, $p = 0.12$
Cortisol	0.42, $p = 0.02$	0.29, $p = 0.12$	0.37, $p = 0.04$	0.30, $p = 0.10$	**0.57**, $\boldsymbol{p = 0.001}$	**0.51**, $\boldsymbol{p = 0.003}$
Stress	0.35, $p = 0.05$	−0.05, $p = 0.81$	−0.05, $p = 0.81$	0.17, $p = 0.35$	0.15, $p = 0.43$	0.01, $p = 0.94$
Mood	0.21, $p = 0.25$	**0.60**, $\boldsymbol{p < 0.001}$	**0.59**, $\boldsymbol{p = 0.001}$	**0.72**, $\boldsymbol{p < 0.001}$	**0.74**, $\boldsymbol{p < 0.001}$	**0.61**, $\boldsymbol{p < 0.001}$

Bonferroni corrected $\alpha = 0.008$.

is also likely to impact the time course of response. For the TSST, ACTH and cortisol peaks are seen on the immediate and 5-min measurement. For the CPT, the response peak is seen at the 5- and 30-min measurement. The ideal comparison would be to have an anticipatory period before a physical stressor combined with a task that would allow for 10 min of exposure in order to control for time of exposure (e.g., more than one CPT administration).

Another limitation of this study is inclusion of females in differing phases of the menstrual cycle, as gonadal hormones have been shown to affect HPA axis response (Kirschbaum *et al*., 1999). Also, total cortisol is reported, as plasma cortisol was not fractionated into free and bound. As free cortisol is biologically active and there can be gender differences in cortisol binding, some differences in cortisol response may have been obscured (Kudielka and Kirchbaum, 2005). All subjects completed the CPT first and TSST second. Ideally, the order of task presentation would be counterbalanced; however, this was not possible as the TSST was an ancillary protocol to a larger protocol in which the CPT had to be completed first. However, the baseline data for the two tasks were not significantly different which argues against a large impact of order of task presentation on stress levels or stress activation.

In conclusion, the results of this preliminary investigation demonstrate that a social stressor resulted in a greater increase in HPA activity as compared to a physical stressor. However, the CPT may have specific utility in differentiating between group differences in diagnostically heterogeneous patients. Further studies are needed to help elucidate these differences and determine if this divergent response to different types of stressors exists in other clinical populations.

REFERENCES

Adinoff B, Martin PR, Bone GHA, *et al*. 1990. Hypothalamic-pituitary-adrenal axis functioning and cerebrospinal fluid corticotropin releasing hormone and corticotropin levels in alcoholics after recent and long-term abstinence. *Arch Gen Psych* **47**: 325–330.

Bernardy NC, King AC, Parsons OA, Lovallo WR. 1996. Altered cortisol response in sober alcoholics: an examination of contributing factors. *Alcohol* **13**: 493–498.

Blake DD, Weathers FW, Nagy LM, *et al*. 1995. The development of a clinician-administered PTSD scale. *J Trauma Stress* **8**: 75–90.

Blandini F, Martignoni E, Sances E, Bono G, Nappi G. 1995. Combined response of plasma and platelet catecholamines to different types of short-term stress. *Life Sci* **56**: 1113–1120.

Bullinger M, Naber D, Pickar D, *et al*. 1984. Endocrine effects of the cold pressor test: relationships to subjective pain appraisal and coping. *Psychiatry Res* **12**: 227–233.

Childress AR, McLellan AT, O'Brien CP. 1986. Abstinent opiate abusers exhibit conditioned craving, conditioned withdrawal and reductions in both through extinction. *Br J Addict* **81**: 655–660.

Costa A, Bono G, Martignoni E, Merlo P, Sances G, Nappi G. 1996. An assessment of hypothalamo-pituitary-adrenal axis functioning in non-depressed, early abstinent alcoholics. *Psychoneuroendocrinology* **21**: 263–275.

Dickerson SS, Kemeny ME. 2004. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol Bull* **130**: 355–391.

Edelson JT, Robertson GL. 1986. The effect of the cold pressor test on vasopressin secretion in man. *Psychoneuroendocrinology* **11**: 307–316.

Ehrenreich H, Schuck J, Stender N, *et al*. 1997. Endocrine and hemodynamic effects of stress versus systemic CRF in alcoholics during early and medium term abstinence. *Alcohol Clin Exp Res* **21**: 1285–1293.

Errico AL, Parsons OA, King AC, Lovallo WR. 1993. Attenuated cortisol response to biobehavioral stressors in sober alcoholics. *J Stud Alcohol* **54**: 393–398.

First MB, Spitzer RL, Gibbon M, Williams JBW. 1994. *Structured Clinical Interview for Axis I DSM-IV Disorders—Patient Edition (SCID-I/P, vs 2.0)*. Biometrics Research Department: New York.

Friedman MJ, Charney DS, Deutch AY (eds). 1995. *Neurobiological and Clinical Consequences of Stress: From Normal Adaptation to PTSD*. Lippincott-Raven: Philadelphia, 576.

Heinz A, Rommelspacher H, Graf KJ, Kurten I, Otto M, Baumgartner A. 1995. Hypothalamic-pituitary-gonadal axis, prolactin, and cortisol in alcoholics during withdrawal and after three weeks of abstinence: comparison with healthy control subjects. *Psychiatry Res* **56**: 81–95.

Herman JP, Cullinan WE. 1997. Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. *Trends Neurosci* **20**: 78–84.

Kelly CB, Cooper SJ. 1998. Plasma norepinephrine response to a cold pressor test in subtypes of depressive illness. *Psychiatry Res* **81**: 39–50.

Kirschbaum C, Kudielka BM, Gaab J, Schommer NC, Helhammer DH. 1999. Impact of gender, menstrual cycle phase, and oral contraceptives on the hypothalamus-pituitary-adrenal axis. *Psychosom Med* **61**: 154–162.

Kirschbaum C, Pirke KM, Hellhammer DH. 1993. The 'Trier Social Stress Test'—a tool for investigating psychobiological stress responses in a laboratory setting. *Neuropsychobiology* **28**: 76–81.

Kudielka BM, Kirchbaum C. 2005. Sex differences in HPA axis response to stress: a review. *Biol Psychiatry* **69**: 113–132.

Lovallo WR, Dickensheets SL, Myers DA, Thomas TL, Nixon SJ. 2000. Blunted stress cortisol response in abstinent alcoholic and polysubstance-abusing men. *Alcohol Clin Exp Res* **24**: 651–658.

Murberg MM (ed.). 1994. *Catecholamine Function in Post-Traumatic Stress Disorder*. American Psychiatric Press: Washington DC, 371.

Pascualy M, Petrie EC, Brodkin K, Peskind ER, Wilkinson CW, Raskind MA. 2000. Hypothalamic pituitary adrenocortical and sympathetic nervous system responses to the cold pressor test in Alzheimer's disease. *Biol Psychiatry* **48**: 247–254.

Peters ML, Godaert GL, Ballieux RE, *et al*. 1998. Cardiovascular and endocrine responses to experimental stress: effects of mental effort and controllability. *Psychoneuroendocrinology* **23**: 1–17.

Resnick HS, Yehuda R, Pittman RK, Foy DW. 1995. Effect of previous trauma on acute plasma cortisol level following rape. *Am J Psychiatry* **152**: 1675–1677.

Velasco M, Gomez J, Blanco M, Rodriguez I. 1997. The cold pressor test: pharmacologic and therapeutic aspects. *Am J Ther* **4**: 34–38.

Vescovi PP, DiGennaro C, Coiro V. 1997. Hormonal (ACTH, Cortisol, β-Endorphin, and Met-Enkephalin) and cardiovascular responses to hyperthermic stress in chronic alcoholics. *Alcohol Clin Exp Res* **21**: 1195–1198.

Yehuda R, Kahana B, Binder-Brynes K, Southwick SM, Mason JW, Giller EL. 1995. Low urinary cortisol excretion in Holocaust survivors with posttraumatic stress disorder. *Am J Psychiatry* **152**: 982–986.

Yehuda R, Southwick SM, Nussbaum G, Wahby V, Giller EL, Jr., Mason JW. 1990. Low urinary cortisol excretion in patients with posttraumatic stress disorder. *J Nerv Ment Dis* **178**: 366–369.

