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## Hippocampal damage abolishes the cortisol response to psychosocial stress in humans

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### ABSTRACT

The hippocampus (HC) is necessary for learning and memory, but it also plays a role in other behaviors such as those related to stress and anxiety. In support of the latter idea, we show here that bilateral HC damage abolishes the cortisol response to psychosocial stress. We collected salivary cortisol, heart rate, and affective responses to the Trier Social Stress Test (TSST) from 7 participants with bilateral HC lesions, 12 participants with damage outside the HC, and 28 healthy normal comparison participants matched to the HC participants on age and sex. HC participants showed elevated pre-stress cortisol, but no cortisol response to the TSST. Heart rate and affective responses in the HC group were similar to those of the comparison groups. Participants with brain damage outside the HC showed stress responses that were comparable to those of the healthy comparison group. These findings support the idea that the functions of the human HC extend beyond learning and memory, and suggest that the HC is necessary for producing the cortisol response to psychosocial stress.

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The hippocampus (HC) is best known for its role in learning and memory (Squire et al., 2004), but it is also involved in other functions, such as stress and anxiety behaviors (see Gray and McNaughton, 2000). The detection of novelty is key both to the formation of new memories (Knight, 1996) as well as to the production of stress responses (Mason et al., 1968; Kirschbaum et al., 1995). HC neurons respond to novel situations (Halgren et al., 1995; Halgren et al., 1980) and HC damage reduces novelty responses (including stress hormone responses) in rodents (Johnson, Moberg, 1980; Kjelstrup et al., 2002). These effects are not based on experience, suggesting that the role of the HC in fear and anxiety is separate from its role in memory. Participants with HC damage do not show a cortisol response to awakening (Buchanan et al., 2004; Wolf et al., 2005). These findings are consistent with the notion that the HC plays a critical role in the regulation of the stress response.

A wealth of research has focused on understanding the regulation of the stress response (Herman et al., 2003; McEwen, 2000; Sapolsky et al., 1986). This work has highlighted the importance of the hypothalamus and pituitary, but many forebrain areas, such as the medial prefrontal cortex and HC, are also involved in the perception of stressors and the initiation of stress responses (Diorio et al., 1993; Feldman et al., 1995; Sapolsky et al., 1984; Kern et al., 2008; Pruessner et al., 2008). Studies have shown that HC lesions can lead to a transient hypersecretion

of GCs (Fischette et al., 1980; Sapolsky et al., 1991; Herman et al., 1998). These findings have led to the idea that the HC plays an inhibitory role over the HPA axis. However, more recent work has suggested that damage restricted to the HC does not lead to increased stress-induced HPA activity (Tuvnes et al., 2003). Tuvnes et al. (2003), in fact, found that under some conditions, HC damage led to decreased GC release, perhaps by reducing fear responses (ala Bannerman et al., 2004; Deacon et al., 2002; Kjelstrup et al., 2002). The effects of HC lesions on emotional responses in humans have not been directly studied.

Considerable work has focused on the deleterious effects of stress on the brain, particularly on the HC via the 'glucocorticoid cascade hypothesis' (Sapolsky et al., 1986). The converse relationship, namely the effects of brain damage on the stress response, has received much less attention. The goal of the current study was to assess the effects of HC damage on the response to psychosocial stress in humans. We examined stress responses to the Trier Social Stress Test (TSST), in participants with bilateral HC damage. Stress responses were measured using salivary cortisol, heart rate, and subjective reports of affect. These measures allow for assessment of physiological and behavioral stress output systems, which are under the control of separate, yet overlapping, neural systems. Based on our previous work (Buchanan et al., 2004), which showed that HC damage abolished the cortisol response to awakening, we hypothesize that the HC is necessary for the cortisol response both to awakening and to psychosocial stress. Based on this hypothesis, we predict that HC damage will also abolish the cortisol response to the TSST.

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## Materials and methods

### Participants

Seven participants with bilateral HC damage and 12 participants with brain damage outside the temporal lobe participated in the study (see Table 1). The brain damaged comparison (BDC) participants had damage outside the medial temporal lobe due to stroke. This group included 3 participants with lateral temporal lobe damage, 5 with parietal lobe damage, and 4 with occipital lobe damage. Comparison participants were 28 healthy volunteers matched to the brain damaged participant groups on age and sex distribution (see Table 1). All brain injured participants were selected from the Patient Registry of the Division of Cognitive Neuroscience at the University of Iowa. Participants were excluded from the current study if they were taking medications that may affect cortisol levels (e.g., any steroid-based drug such as prednisone or estrogen/progesterone hormone replacement or oral contraceptives). Smokers were excluded from participation, as smokers show attenuated response to laboratory stressors (Kirschbaum et al., 1993b).

All HC participants had defective anterograde memory. There is variability in the extent of HC damage and anterograde amnesia in the HC group; however, every participant in the HC group incurred some damage to the HC bilaterally (see Fig. 1) due to either anoxia or encephalitis, and was left with at least mild anterograde amnesia.

### Neuroanatomical data

Magnetic resonance images were obtained from 4 HC<sup>1</sup> participants in a 1.5 T General Electric scanner (see Fig. 1a). The scanning protocol used in this study is identical to that used in previous work from our laboratory (Allen et al., 2002; Buchanan et al., 2004). All brains were reconstructed in three dimensions in Brainvox (Frank et al., 1997), and regions were traced by hand on contiguous coronal slices of the brain.

The remaining volumes of the hippocampus and amygdala were traced in both hemispheres of each participant. Volumes of the amygdala were included because of this structure's role in stress and emotion processing (Adolphs, 2002). Criteria for the boundaries of both the amygdala and hippocampus were derived from the atlas of Duvernoy (1988). Using a method similar to that of Convit et al. (1999), pointsets delineating the boundaries of the amygdala and hippocampus were first made in parasagittal and axial planes; these pointsets were then projected to the coronal slices to guide tracing of the ROIs.

Data from a normative sample of age- and gender-matched comparison participants described in Allen et al. (2005) were used to examine reductions in hippocampal and amygdala volumes of the HC participants. Data from these comparison participants were collected using the same scanner specifications and procedures as those used in the current study. To control for age and gender influences on brain volume, the differences between lesioned and comparison brains were converted to studentized residuals (actual value minus expected value) based on equations that model age- and gender-related effects in brain structure (Allen et al., 2006). Studentized residuals greater than 2.0 were significant at the  $p < 0.05$  level and 2.66 denotes difference at the  $p < 0.01$  level (see Table 1; Allen et al., 2006). Of the 4 HC participants whose MRI data were available, 3 showed significantly reduced HC volume (see Table 1). The HC volume of patient 2607 was low (studentized

residual of  $-1.19$ ), but was not significantly different from the comparison sample. By contrast, none of the HC participants showed significantly reduced amygdala volume using the same analysis procedure. Total volume of left and right hippocampus and amygdala collapsed across hemispheres are presented in Table 1.

### Protocol

Participants completed an informed consent document approved by the University of Iowa IRB. The Trier Social Stress Test (TSST) was then introduced to the participant. The TSST is a widely used, reliable stressor (Kirschbaum et al., 1993a) consisting of an anticipation period (10 min) and a test period (10 min) during which participants deliver a speech and perform mental arithmetic in front of an 'audience' of experimenters. Participants were randomly assigned to one of two scenarios on which to base their speech: a mock job interview ( $N = 24$ ) or a mock accusation of shoplifting ( $N = 23$ ). Cortisol responses to the two scenarios did not differ across the whole sample ( $F < 1$ ,  $p > 0.3$ ), nor were there differences in responses to the 2 scenarios within the participant groups (no Group  $\times$  Scenario interaction:  $F < 1$ ,  $p > 0.5$ ). After preparation, the participant was escorted to a conference room where the speech and math portion of the task were completed. Two experimenters were present during the TSST and the participant was videotaped throughout.

Saliva samples were obtained using a commercially available collection device (Salivette<sup>®</sup>, Sarstedt, Rommelsdorf, Germany). Samples were taken at 3 time points: 15 min after arrival in the laboratory, 10 and 30 min after the end of the TSST. Samples were stored at  $-20^\circ\text{C}$  until assayed. Salivary cortisol was measured with a commercial immunoassay kit (CLIA, IBL Hamburg, Germany). Intra-assay and interassay coefficients of variation were less than 10%.

Subjective responses to the TSST were collected using two scales: the Positive Affect/Negative Affect Schedule (PANAS; Watson et al., 1988) and the Primary Appraisal/Secondary Appraisal scale (PASA; Gaab et al., 2005). Heart rate was measured throughout the testing protocol, including during a 15 min baseline period prior to introduction to the TSST, as well as during the preparation and performance of the TSST.

### Data analysis

Cortisol data were analyzed using a 3 Group (HC, BDC, healthy comparison)  $\times$  2 Sex  $\times$  3 Sample (pre-TSST, TSST + 10 min, TSST + 30 min) ANOVA with repeated measures on the Sample factor. Sex was included as a factor in these analyses because men tend to show greater laboratory stress responses than women (Kudielka and Kirschbaum, 2005). Measures of effect size are reported using eta-squared ( $\eta^2$ ). Similar analysis strategies were used for heart rate and subjective responses to the TSST (described below).

## Results

### Participant and testing characteristics

Participant characteristics, including neuroanatomical data are presented in Table 1. The groups did not differ in age, education, or chronicity of brain injury ( $ps > 0.17$ ). Due to the diurnal cycle of cortisol, we examined the relationship between time of testing and cortisol response by comparing starting times across groups. The groups did not differ in average start time (mean start time for HC group:  $09:53 \pm 59$  min; BDC group:  $09:47 \pm 25$  min; NC group:  $09:51 \pm 12$  min;  $F(2,44) < 1$ ). These findings demonstrate that each participant completed the task at roughly the same time of day; previous work has shown that although cortisol levels are higher in the morning than in the afternoon, the cortisol response is consistent across different times of day (Kudielka et al., 2004).

<sup>1</sup> Volumetric data from 3 HC patients (2563, 3139, and 3344) are not available, due to the fact that since these patients wear pacemakers, they cannot have an MR study (CT scans were used instead to characterize their lesions; see Fig. 1b). Inspection of these patients' CT scans revealed volume reductions in the hippocampus, but we were not able to quantify the damage due to the relatively low resolution of CT. Nonetheless, the observation of HC volume reduction along with the etiology (anoxia) and cognitive profile (amnesia) strongly suggest that these individuals have considerable loss of hippocampal volume.

**Table 1**  
Demographic and neuroanatomical data.

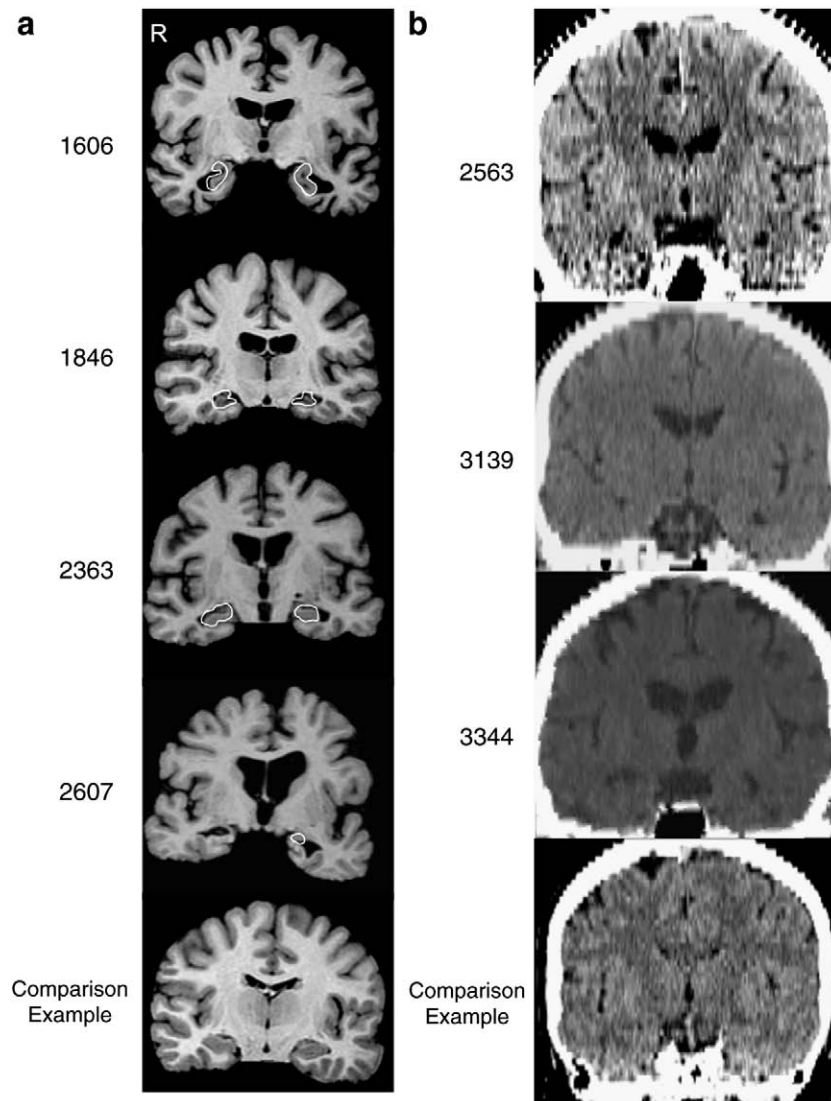
Group	Age	Sex	Education	Etiology	Years since onset	HC volume	HC residual	Amygdala volume	Amygdala residual
HC									
1606	57	M	12	Anoxia	15	4190	−3.99 <sup>b</sup>	3010	−1.18
1846	41	F	14	Anoxia	12	3474	−4.23 <sup>b</sup>	2220	−0.90
2363	48	M	16	Anoxia	7	5110	−2.64 <sup>a</sup>	3380	−0.60
2563	49	M	16	Anoxia	6	NA	NA	NA	NA
2607	75	F	14	HSE	5	4166	−1.19	1504	0.10
3139	52	M	20	Anoxia	0.7*	NA	NA	NA	NA
3344	25	F	12	Anoxia	2	NA	NA	NA	NA
HC summary	50.0 ± 15.4	3 F/4 M	14.9 ± 2.8	Mixed	6.9 ± 5.1	4235 ± 671.4	−3.62 ± 1.4	2529 ± 836.9	−0.89 ± 0.6
BDC (N = 12)	56.3 ± 10.4	6 F/6 M	13.9 ± 3.1	Mixed	8.7 ± 6.5	–	–	–	–
NC (N = 28)	54.2 ± 10.7	14 F/14 M	15.9 ± 2.5	–	–	–	–	–	–

HC = hippocampal lesion participants, BDC = brain damaged comparison participants, NC = normal comparison participants. \*Tested 8 months after anoxic event. Entries show mean ± standard deviation. HSE = herpes simplex encephalitis. Studentized residuals greater than |2.0| were significant at the  $p < 0.05^a$  level and |2.66| denotes difference at the  $p < 0.01^b$  level (see Allen et al., 2006).

### Cortisol responses

Fig. 2 shows the cortisol levels across groups and Fig. 3 shows the cortisol levels across all samples for each individual HC lesion patient. The HC group had higher pre-stress cortisol levels compared to the NC

group ( $p < 0.05$ ), but not the BDC group ( $p > 0.6$ ). In contrast to both comparison groups, the HC group failed to show a cortisol response to the task (Group by Sample interaction:  $F(4,82) = 4.7, p < 0.01, \eta^2 = 0.19$ ). Post-hoc contrasts show that the HC group's response was significantly lower than both the NC group ( $p < 0.01$ ) and the BDC group ( $p < 0.05$ ).



**Fig. 1.** (a) Neuroanatomy of 4 participants with hippocampal lesions and from a representative healthy brain from MR scans. White outlines indicate hippocampal region-of-interest traced on each representative slice. Note that the right hippocampus in participant 2607 was not visible in this slice. (b) Neuroanatomy of 3 participants with hippocampal lesions and one from a representative healthy brain from CT scans.

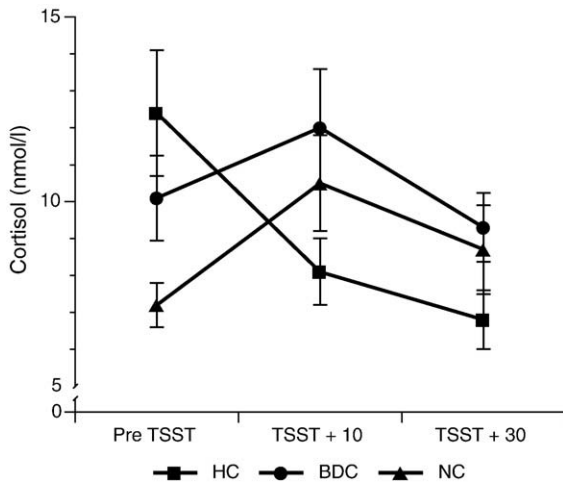


Fig. 2. Cortisol levels across groups. Data show mean ( $\pm$ SEM) of cortisol levels before, 10 min, and 30 min after the Trier Social Stress Test (TSST) in the hippocampal group (HC), the brain damage comparison group (BDC), and normal comparison group (NC).

In order to examine each group's cortisol response to the task, simple repeated measures analyses, along with polynomial contrasts to test the pattern of response (linear versus quadratic), were run within each group. Based on the typical response to the TSST, we predicted a significant quadratic trend in cortisol response in the comparison groups, indicating an increase in response from sample one to sample two and a decrease from sample two to sample three. Results from the NC group showed a significant cortisol response and the expected quadratic pattern (Main effect:  $F(2,26) = 6.6, p = 0.005, \eta^2 = 0.34$ ; Quadratic trend:  $F(1,27) = 10.0, p = 0.004, \eta^2 = 0.27$ ). Similarly, the BDC group showed a significant main effect,  $F(2,10) = 6.9, p = 0.013, \eta^2 = 0.58$ , and quadratic pattern,  $F(1,11) = 4.8, p = 0.05, \eta^2 = 0.3$ . By contrast, the HC group showed a non-significant main effect,  $F(2,5) = 4.4, p = 0.08, \eta^2 = 0.638$ , but did not show the quadratic pattern. The HC group, however, showed a significant linear pattern of decreasing cortisol across the 2 post stress samples ( $F(1,6) = 9.4, p = 0.02, \eta^2 = 0.6$ ). Across all groups, there was a trend toward a significant effect of Sample,  $F(2,82) = 3.4, p = 0.06, \eta^2 = 0.08$ . As anticipated from previous research (Kudielka and Kirschbaum, 2005), men showed a trend toward greater cortisol response than women (Sex by Sample interaction:  $F(2,82) = 3.4, p = 0.06, \eta^2 = 0.08$ ).

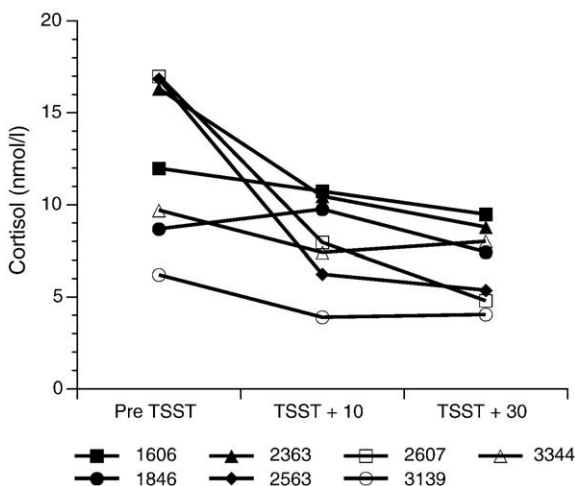


Fig. 3. Cortisol levels from all participants in the HC group. Data show cortisol levels before, 10 min, and 30 min after the Trier Social Stress Test (TSST).

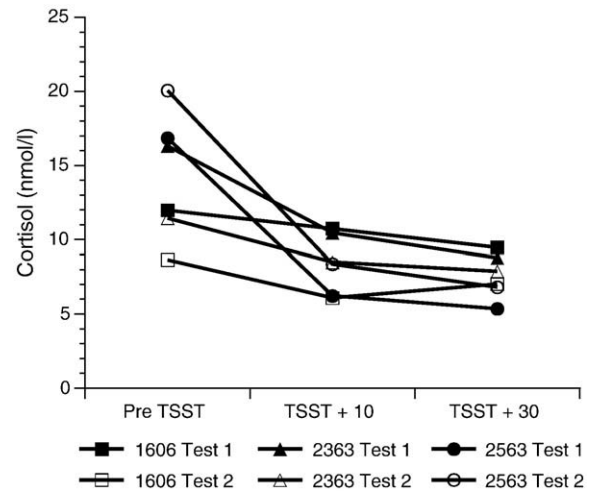


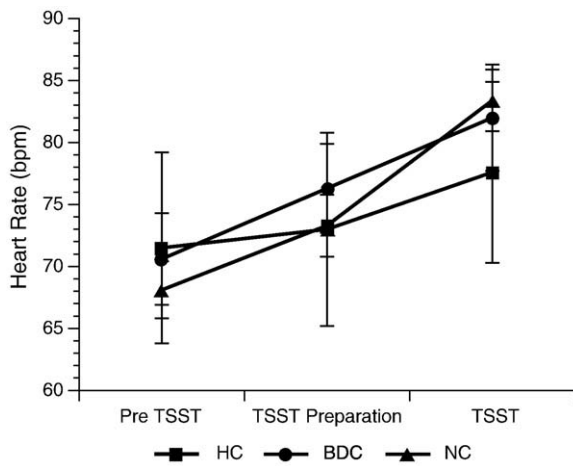
Fig. 4. Cortisol levels across testing sessions for 3 hippocampal lesion patients tested twice on the TSST. Data show cortisol levels before, 10 min, and 30 min after the Trier Social Stress Test (TSST) from both testing session for each individual.

Previous work has shown that approximately 70% of healthy individuals show a cortisol stress response to laboratory stressors such as the TSST (Kirschbaum et al., 1993a). Differences in response patterns across groups in the current study could be driven by the response (or the lack of response) of only a few individuals. For example, the mean reduction in cortisol in the HC group could be due to one individual showing a marked reduction, while the others in the group showed increases. We tested this possibility by examining the number of cortisol responders across groups. The percentage of responders by group were: HC: 17% (1 out of 7); BDC group: 67% (8 out of 12); and NC: 68% (19 out of 28). This difference in response pattern was statistically significant,  $\chi^2(2) = 7.0, p < 0.05$  (and the overall response rates in the BDC and normal groups are similar to typical population base rates). The one HC participant to produce a cortisol increase to the TSST showed an increase of 1.07 nmol/l. By contrast, the average response of the NC group and BDC group was 3.3 and 1.9 nmol/l, respectively.

In order to assess the reliability of the lack of cortisol response to the TSST in the HC participants, 3 of these participants were tested twice (one participant at an interval of 3 months, the other two at 7 months after initial testing). In the second phase testing, the participants were tested at the same time of day, in a different room and were asked to give a different speech (either the job interview or shoplifting scenario, whichever they had not completed during the first testing session). These participants showed a similar pattern of response across the testing sessions (see Fig. 4). The mean cortisol response from the first session was  $-5.9$  (sd: 4.7) and the mean from the second session was  $-5.7$  (sd: 5.2) nmol/l.

Heart rate

Heart rate responses to the TSST were analyzed using a 3 Group  $\times$  2 Sex  $\times$  3 Sample (Baseline, TSST preparation, TSST performance) ANOVA (see Fig. 5). All groups showed increased heart rate throughout the task,  $F(2,72) = 27, p < 0.0001, \eta^2 = 0.43$ . There was a significant Group by Sample interaction,  $F(4,72) = 2.9, p < 0.05, \eta^2 = 0.14$ . This interaction may be due to a lower heart rate by the NC group during the baseline and preparation periods. The groups show similar heart rate responses to the TSST (no post-hoc differences in heart rate during the TSST,  $ps > 0.7$ ). There was no main effect of group,  $p > 0.8$ , there was, however a trend toward women showing a higher heart rate than men,  $F(1,36) = 3.7, p = 0.06, \eta^2 = 0.09$ . There was not a significant group by sex interaction, however ( $p > 0.3$ ). These results demonstrate intact HR responses in HC damaged individuals despite a lack of a stress cortisol response.



**Fig. 5.** Heart rate across groups. Data show mean ( $\pm$  SEM) of heart rate during baseline, Trier Social Stress Test (TSST) preparation, and during the TSST in the hippocampal group (HC), the brain damage comparison group (BDC); and normal comparison group (NC).

### Subjective reports

Ratings of positive (PA) and negative affect (NA) were analyzed by comparing ratings before and after the TSST across groups (see Table 2). All groups increased their NA ratings in response to the TSST,  $F(1,41) = 38$ ,  $p < 0.0001$ ,  $\eta^2 = 0.48$ . The groups showed a different pattern of response, however (Group by Time interaction:  $F(2,50) = 4.2$ ,  $p < 0.05$ ,  $\eta^2 = 0.14$ ), with the HC group reporting a greater increase in NA than both comparison groups. There were no group differences in pre-stress negative affect. These results demonstrate that the HC participants reported greater NA in response to the TSST, despite failing to show a cortisol response. There were no group differences in PA ratings,  $F(2,41) < 1$ ,  $p > 0.4$ ,  $\eta^2 = 0.04$ , nor were there differences in PA ratings from before versus after the task (no Group by Time interaction:  $F < 1$ ).

There were no group differences in ratings of any of the scales on the PASA (ps range from 0.1 to 0.8). None of the post-hoc tests were significant. These results suggest that the HC group perceived the task normally (i.e., as stressful) in spite of the lack of cortisol response.

### Discussion

Results from this study show that bilateral HC damage abolishes the cortisol response to psychosocial stress. This effect was found in the presence of intact heart rate responses and subjective reports of stress, suggesting that the HC exerts specific control over the HPA axis during stress, but not over the heart nor over affective reports. These findings, along with previous work showing a lack of a cortisol awakening response after HC damage (Buchanan et al., 2004; Wolf et al., 2005), suggest that the HC plays a critical, perhaps even necessary, role in mounting a cortisol response to psychosocial stress. The results also suggest that different channels of the stress response (HPA, autonomic nervous system, and subjective reports) are under separable neural control. This differential control over these channels

may have been predicted by previous work demonstrating a strong cortical generator for autonomic control located in medial prefrontal and insular regions (see Cechetto and Saper, 1987; Critchley, 2005; Oppenheimer, 2006). These cortical regions have not been as closely linked with control over the HPA axis (though see Kern et al., 2008), but the HC is well known to exert control over HPA function (Feldman et al., 1995; McEwen, 2000; Pruessner et al., 2008).

The HC has long been the focus of research on stress, fear, and anxiety (Gray and McNaughton, 2000). Several studies have described reduced fear and anxiety behavior after HC lesions in animals (Kjelstrup et al., 2002; Bannerman et al., 2004; Deacon et al., 2002; Chudasama et al., 2008). The HC shows increased activity in response to novelty (Halgren et al., 1995; Halgren et al., 1980), and HC damage reduces novelty responses in humans and nonhuman animals (Johnson and Moberg, 1980; Kishiyama et al., 2004; Knight, 1996). Glucocorticoid responses to laboratory stress rely, at least to some degree, on novelty. Monkeys show reduced glucocorticoid responses to repeated stressful avoidance sessions (Mason et al., 1968). Healthy human participants repeatedly tested on the TSST show reduced cortisol responses to repeated testing (Kirschbaum et al., 1995). Sympathetic nervous system indices do not show this habituation (Schommer et al., 2003). These results, along with those from the current investigation showing a dissociation in reactivity of the HPA axis and the heart, suggest a differential neural control over the HPA and sympathetic responses to stress.

Findings from the current study and our previous work (Buchanan et al., 2004) demonstrate that participants with HC damage do not produce a cortisol response to either psychosocial stress or awakening. Participants with HC damage do show the normal diurnal pattern of cortisol after the awakening response—peaking in the morning and diminishing throughout the day (Buchanan et al., 2004; Wolf et al., 2005). The current results are in line with these findings, demonstrating a lack of a cortisol response to the TSST, but the typical reduction in cortisol levels across testing periods. We interpret the lack of a cortisol response to be a function of the typical diurnal cycle of cortisol: showing a pronounced reduction throughout the day. That these participants show increased ratings of stress demonstrates that subjective feeling states are dissociable from the production of a cortisol response. The HC then may be a necessary component of a network involved in producing an integrated response to psychosocial stress, as indexed by behavior and HPA activity.

Animal research has shown a transient enhancement of glucocorticoid secretion after medial temporal lobe damage including the HC, which returns to normal within 1–2 weeks in rats (Fischette et al., 1980) and within 6–15 months in monkeys (Sapolsky et al., 1991). The time between damage and testing in our participants (tested at an average of 8.7 years after brain damage; range, 8 months to 32 years) are well beyond these time frames for recovery of normal glucocorticoid function reported in rats and monkeys. More recent work has shown that selective lesions of the HC and subiculum (even temporarily) do not increase glucocorticoid release in rats (Tuvnes et al., 2003). These findings suggest that although large medial temporal lesions including the HC may cause transient glucocorticoid hypersecretion, damage limited to the HC does not. Participants included in the present study were all within the chronic epoch. Six of the seven HC damaged participants had damage due to anoxia (the

**Table 2**  
Subjective ratings performance.

Group	Pre-stress negative affect	Post-stress negative affect	Pre-stress positive affect	Post-stress positive affect	Threat	Challenge	Self-concept	Control expectancy
HC	14.1 $\pm$ 1.7	24.0 $\pm$ 3.5*	32.4 $\pm$ 2.5	36.4 $\pm$ 2.9	1.5 $\pm$ 0.3	4.0 $\pm$ 0.5	3.6 $\pm$ 0.3	4.7 $\pm$ 0.3
BDC	15.3 $\pm$ 1.2	20.5 $\pm$ 1.7	31.2 $\pm$ 1.6	31.7 $\pm$ 1.6	2.0 $\pm$ 0.3	3.7 $\pm$ 0.3	3.7 $\pm$ 0.3	4.1 $\pm$ 0.3
NC	12.1 $\pm$ 0.5	15.5 $\pm$ 0.9	33.8 $\pm$ 1.1	33.5 $\pm$ 1.4	2.1 $\pm$ 0.2	3.7 $\pm$ 0.2	4.2 $\pm$ 0.2	4.5 $\pm$ 0.2

Entries show mean  $\pm$  standard error of the mean. Positive and negative affect were collected using the Positive Affect/Negative Affect Schedule (PANAS). Threat, Challenge, Self-Concept, and Control Expectancy were collected using the Primary Appraisal/Secondary Appraisal scale (PASA).

\* Indicates a significant group by time interaction in negative affect ( $p < 0.05$ ).

other's damage was due to encephalitis). Anoxia affects the structure of other brain areas, including the volume of gray matter throughout the cerebrum, but the HC is the structure that is most reduced in volume following anoxic injury (Allen et al., 2006). The BDC participants in the current study, by contrast, had variable damage to the lateral temporal, parietal, or occipital cortices; these participants showed normal cortisol stress responses. Together, these findings suggest that regardless of the extent of extrahippocampal damage, bilateral reductions in HC volumes results in a drastic reduction in cortisol response to stress.

Tuvnes et al. (2003) demonstrated that HC damage in rats reduced corticosterone responses to mild and moderate stressors. By contrast, Tuvnes et al., (2003) and others (Bangasser and Shors, 2007) have shown that HC lesioned rats do show corticosterone responses to severe stressors such as restraint protocols. The HC may be necessary to produce the glucocorticoid response to mild stressors, but severe stress may recruit other neural regions, resulting in a normal stress response. The intensity of the stress induced by the TSST is mild by comparison to animal stress testing. The possibility remains, therefore, for more severe stress to produce a cortisol response in our participants, perhaps in response to real-world stressful situations.

The HC participants' pre-stress cortisol levels were significantly higher than the normal comparison participants. This high pre-stress level could result in less of a cortisol response due to negative feedback at the level of the hypothalamus, which may have acted to reduce the drive of the HPA axis. We cannot rule out this possibility, but our data clearly demonstrate an altered pattern of cortisol release in individuals with HC damage to a task that results in increased cortisol in most individuals. The pattern of reduced cortisol levels in the HC group from pre- to poststress samples is most likely due to the normal circadian decrease in cortisol throughout the day. A recent study in our lab, which measured cortisol in healthy participants at the same time of day and at the same intervals in the current study showed a very similar pattern of cortisol reduction across samples (Buchanan and Tranel, 2008).

The extent to which the HC participants' amnesia affected responding to the task is not certain. Each of the HC participants showed anterograde memory disturbance. All of these participants reported increased subjective ratings of stress in anticipation of, and after the task. Pre-task anticipation ratings were collected immediately before the task, often after participants had been reminded of the task instructions, within the participants' limited memory span. Similarly, post-task ratings were collected immediately after completion of the TSST. The timing of these ratings were within the range of these participants' memory spans (based on neuropsychological test performance, see Tranel et al., 2000); their ratings should accurately reflect their responses to the task. Another question that arises is: did the HC participants engage in the task? The HC lesion participants showed subjective responses that were comparable to the other participants (HC participants in fact rated the task as more negatively affective than the other groups). Finally, three of the HC participants were tested twice and showed remarkable consistency of response across both testing sessions (see Fig. 4). These findings support the contention that these participants were engaged with the task, described the task as stressful, but were unable to produce a cortisol response.

Many studies have addressed the effects of stress and glucocorticoids on the structure and function of the hippocampus and more recent work has suggested a role for the human hippocampus in the control of the cortisol stress response (Pruessner et al., 2008). This is the first study, to our knowledge, to address the effects of HC damage on the human stress response. Damage to the hippocampus abolishes the cortisol response to a psychosocial stressor while heart rate and affective responses remain intact. These findings demonstrate that, beyond its traditional role in memory processing, the hippocampus plays an important role in the production of the response to psychosocial stress.

#### Conflict of interest statement

None of the authors has to declare any conflict of interest, financial or otherwise.

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