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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.

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[1] 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 × 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®, 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 °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) × 2 Sex × 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 (η^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 ± 59 min; BDC group: 09:47 ± 25 min; NC group: 09:51 ± 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).

[1] 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.