

Circadian Regulation of Cortisol After Hippocampal Damage in Humans

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Background: *There is substantial evidence that the hippocampus (HC) regulates the activity of the hypothalamic–pituitary–adrenocortical (HPA) axis. Damage to the HC in animals produces a transient alteration in diurnal and stress-related HPA activity. This study was designed to examine the effects of HC damage on basal cortisol secretion in humans.*

Methods: *Salivary cortisol was measured in 22 patients with HC damage (12 with bilateral damage and 10 with unilateral damage), 7 brain-damaged comparison participants, 10 healthy, age-matched comparison participants, and 6 of the patients' caregivers. Salivary cortisol samples were taken immediately after awakening, 30 min after awakening, at 8:00 AM, 11:00 AM, 3:00 PM, 6:00 PM, and at bedtime on a single day. Brain-injured patients underwent a structural magnetic resonance imaging scan to examine quantitative volumes of the HC.*

Results: *Both bilateral and unilateral HC damage abolished the cortisol response to awakening documented in the comparison groups. Caregivers of bilateral HC patients showed a reduced response to awakening. The remainder of the circadian pattern was not affected in the HC patients; all groups showed a significant diurnal variation. There was no association between HC volume and cortisol secretion.*

Conclusions: *Hippocampal damage in humans abolishes the cortisol response to awakening, whereas the remainder of the diurnal cycle is unaffected in these patients. These data suggest a unique role of the HC in the control of basal cortisol secretion.*

Key Words: Cortisol, hippocampus, HPA axis, amygdala, medial temporal lobe

Since the finding that corticosteroids bind to the hippocampus (HC) (McEwen et al 1968), the role of this structure in the regulation of the hypothalamic–pituitary–adrenocortical (HPA) axis has been examined extensively in animals (see also Kim and Diamond 2002; McEwen 2000 for review). Whereas the paraventricular nucleus of the hypothalamus and pituitary are the primary targets of glucocorticoid negative feedback (Dallman et al 1987), the HC exerts influence on the HPA axis through regulation of forebrain activity (de Kloet et al 1999; Oitzl et al 1997). The occupation of corticosteroid receptors reduces the release of corticotropin-releasing hormone and adrenocorticotrophic hormone at the level of the hypothalamus and anterior pituitary, respectively (Dallman et al 1987). This reduction in secretagogue activity turns off the release of corticosteroids from the adrenal cortex. Both types of corticosteroid receptors (mineralocorticoid and glucocorticoid receptors) are found in large numbers in the rodent hippocampus (Reul and de Kloet 1985; although see Watzka et al 2000 and Sanchez et al 2000 for discussion of the distribution of these receptors in the primate brain).

The alteration in the level and distribution of mineralocorticoid and glucocorticoid receptors in the brain after HC lesion might alter the pattern of basal and/or stress-induced cortisol secretion. In both rats (Fendler et al 1961) and nonhuman primates (Sapolsky et al 1991), HC lesions result in a transient glucocorticoid hypersecretion that returns to normal after a period of time. Numerous studies have documented a relationship between hippocampal volume and cortisol levels in hu-

mans. These findings come from studies of posttraumatic stress disorder (PTSD; Yehuda 2001), normal aging (Lupien et al 1998; Wolf et al 2002), Cushing's disease (Starkman et al 1992, 1999), and Alzheimer's disease (de Leon et al 1988). Lupien et al (1998) demonstrated that in otherwise healthy aging individuals, a subgroup with higher basal cortisol levels showed reduced hippocampal volume and impaired declarative memory performance. Extending these findings to a younger population, Cho (2001) showed that the frequent cortisol elevations associated with jet lag result in temporal lobe atrophy and reduced declarative memory performance in young (22- to 28-year-old) flight attendants (Cho 2001).

Although these studies suggest an association between the HC and HPA activity in humans, no studies to date have addressed the effect of overt HC damage on the level and pattern of cortisol secretion in humans. Altered HPA function in patients with HC damage could have deleterious effects on both physical and mental health. Therefore, the present study examined the association between HC damage and the pattern of cortisol secretion in humans. We examined the cortisol response to awakening, the diurnal cycle of cortisol, and the relationship between HC volume and cortisol levels in patients with bilateral and unilateral HC damage. Comparison participants included patients with brain damage not including the medial temporal lobe, age-matched healthy comparison participants, and caregivers of patients with bilateral HC damage. This latter group was included to examine the HPA concomitants of caregiving for a patient with neurologic damage resulting in amnesia (see Da Roza Davis and Cowen 2001).

Methods and Materials

Subjects

Twenty-two patients with HC damage, seven patients with brain injury outside the medial temporal lobe, 10 healthy comparison participants, and six caregivers of the patients participated in this study. Among those patients with damage to the HC, six had brain damage due to encephalitis, all of whom had bilateral damage to the medial temporal lobe, including the hippocampus, amygdala, and surrounding cortex (Tranel et al

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Table 1. Characteristics of Patients and Comparison Participants

Patient	Age (y)	Gender	HC Volume (mm ³)	Amygdala Volume (mm ³)	Years Since Onset	Cortisol AUC Test 1 (nmol/L)	Cortisol AUC Test 2 (nmol/L)	Wake Cortisol Response
Bilateral (n = 12)	53.1 ± 15.9	9M/3F	3668 ± 2348	1703 ± 1602	6.8 ± 6.0	65.3 ± 20.7	76.3 ± 28.4	-1.3 ± 9.0
Unilateral (n = 10)	48.6 ± 9.7	2M/8F	5854 ± 1289	2245 ± 554	6.7 ± 8.4	70.5 ± 45.4		.01 ± 15.3
BDC (n = 7)	54.4 ± 12.0	4M/3F	8258 ± 513	3321 ± 503	4.9 ± 4.5	94.4 ± 49.7		18.0 ± 31.8
Caregivers (n = 6)	63.8 ± 13.4	2M/4F				64.6 ± 38.1		6.0 ± 9.8
Control Participants (n = 10)	56.1 ± 12.4	5M/5F				69.4 ± 27.5		12.0 ± 10.5

Data are presented as mean ± SD. HC Volume, combined bilateral hippocampal volume; Amygdala Volume, combined bilateral amygdala volume; AUC, area under the curve; M, male; F, female; BDC, brain-damaged comparison subjects.

2000); six had damage due to anoxia, all of whom had bilateral reductions in HC volume confirmed by magnetic resonance imaging (MRI) (Allen et al 2002b); and 10 had unilateral HC damage (six left-sided, four right-sided). Nine of these patients had temporal lobectomy for the treatment of medically intractable epilepsy involving excision of portions of the temporal lobe, including the amygdala and HC. One of the unilateral HC patients had damage due to a left-sided posterior cerebral artery stroke that resulted in damage to the posterior left HC, among other regions. The brain-damaged comparison (BDC) patient group consisted of seven patients with damage to the brain outside of the medial temporal lobe. These patients' brain injuries were due to stroke (right middle cerebral artery stroke, right-sided parietal stroke, left-sided frontoparietal stroke, left frontal infarct), aneurysm clipping (right frontal anterior communicating artery), or meningioma resection (left posterior parietal, bilateral frontal). All brain-damaged participants were selected from the Patient Registry of the Division of Cognitive Neuroscience at the University of Iowa. The inclusion criteria for all patients in the registry include 1) aged 18 years or older; 2) absence of mental retardation, dementia, psychiatric history, and history of alcohol or drug abuse; 3) absence of systemic disease that might affect the central nervous system (CNS) (e.g., primary tumors with potential CNS involvement, uncontrolled diabetes, systemic infections, and other metabolic diseases); 4) singularity of damage site within a hemisphere; 5) type of neuropathologic process (only subjects with cerebrovascular accidents including anoxia, herpes simplex encephalitis, surgical ablation, progressive localized atrophy, and selected instances of cerebral contusion are eligible for induction). An additional exclusion criterion for the current study was the taking of medications that might affect cortisol levels (e.g., any steroid-based drug, such as prednisone or estrogen/progesterone hormone replacement).

Healthy comparison participants were 10 age-matched participants (five women/five men) recruited for participation from the community. The six caregivers (four women/two men) included four spouses and two parents of the severely amnesic patients within the bilateral HC group. These participants were included to assess the possible alteration of HPA function in caregivers of amnesic patients in light of previously reported alteration of cortisol secretion in caregivers of chronically ill patients (Da Roza Davis and Cowen 2001; Irwin et al 1997). See Table 1 for demographic characteristics of all participants. The participants gave informed consent for their involvement in the study, and the experiment described complied with the University of Iowa Institutional Review Board and International Committee of Medical Journal Editors ethical standards for the treatment of participants.

Procedure

All participants provided salivary samples for measure of cortisol over the course of a single day. Saliva sampling was

repeated in five patients with bilateral HC damage at 7 months after initial testing, for validation of circadian rhythms. Saliva samples were obtained with a commercially available collection device (Salivette; Sarstedt, Rommelsdorf, Germany). Instructions for saliva sampling were given in both oral and written form to the patients, caregivers, and comparison participants to reinforce compliance with the timing of the samples. Samples were given immediately upon awakening, 30 min after awakening, at 8:00 AM, 11:00 AM, 3:00 PM, 6:00 PM, and at bedtime. Several studies have documented a cortisol response to awakening and have suggested that this response is a reliable measure of HPA axis integrity (e.g., Pruessner et al 1997; Rohleder et al 2004). Samples were collected both in the hospital and in the patients' and caregivers' hotel rooms or homes. Salivary samples were chosen over blood samples because of the ease of testing in ambulatory settings, to alleviate the inherent stressful nature of blood sampling, and because it gives an accurate measure of circulating free cortisol in the blood (Kirschbaum and Hellhammer 1989).

Structural Neuroimaging

Magnetic resonance images were obtained from 26 of the 29 brain-injured patients (two patients [one bilateral HC, one BDC] received a computed tomography scan, and one patient [bilateral HC] was not scanned at all) in a General Electric 4096 Plus scanner (General Electric Medical Systems, Milwaukee, Wisconsin) operating at 1.5 T. The scanning protocol used in this study was identical to that used previously by Allen et al (2002a). All brains were reconstructed in three dimensions in Brainvox (Frank et al 1997), an interactive family of programs designed to reconstruct, segment, and measure brains from MR-acquired images. An automated program, validated against human experts (Grabowski et al 2000), was used to segment the images into the three primary tissue types (white, gray, cerebrospinal fluid). For the analyses reported here, only the gray matter volumes of the hippocampus and amygdala are reported. All regions were traced by hand on contiguous coronal slices of the brain.

Two regions of interest (ROIs) (if present) were traced in each hemisphere: the hippocampus and the amygdala. Whole brain volumes were also determined. Criteria for the boundaries of both the amygdala and hippocampus were derived from the atlas of Duvernoy (1988). With a method similar to that of Convit et al (1999) (see also Szabo et al 2001), point sets tracing the boundaries of the amygdala and hippocampus were first made in parasagittal and axial planes; these point sets were then projected to the coronal slices to guide tracing of the ROIs.

The hippocampus can be readily identified from the surrounding parahippocampal gyrus, lateral ventricle, and other basal-medial structures. Anteriorly, it is separated from the amygdala by the inferior horn of the lateral ventricle (although the inferior horn can be difficult to see in some subjects, hence the need for point sets made in other orientations), emerging

initially as a structure inferior to the amygdala. Posteriorly, care must be taken to separate the tail of the hippocampus from the fasciolar gyrus, which is a small gyrus that originates on the medial surface near the end of the hippocampus (see Duvernoy 1999). The fimbria, which runs along much of the superior surface of the hippocampus, was included in the hippocampus ROI; however, because white matter volumes were excluded from the volume measurement of the hippocampus, it made no contribution to the reported hippocampal volume.

The amygdala is bounded posteroinferiorly by the hippocampus. In coronal MR images, there are no definitive landmarks to signal the anterior origin of the amygdala. Other researchers (Convit et al 1999; Szabo et al 2001) have used the optic chiasm as a landmark to initiate tracing the amygdala. Because the temporal lobes are rarely bilaterally symmetric, we elected to use a landmark that could be identified independently in each hemisphere, namely the first coronal slice in which there is a definitive connection between the temporal and frontal lobes. This slice was designated as slice 1, and moving posteriorly through the brain, the most anterior amygdala slice was traced on slice 4 (see Duvernoy 1999). The rationale behind this was as follows. In the region of the temporal stem, the uncus forms a cortical “cap” over the anterior amygdala. By starting the amygdala tracing three slices posterior to the frontotemporal junction, we could be certain that we were posterior to the anterior cortex of the gyrus ambiens of the uncus (assuming the cortex in this region is approximately 4 mm thick). Given the inherent variation in the relationship between the slice orientation and the frontotemporal junction, on some occasions the anterior-most slice of the amygdala was traced on slices 3 or 5 beyond the junction, rather than on slice 4. Although as arbitrary as other methods for identifying the anterior limit of the amygdala, this method has the advantage of making use of the local, lateralized anatomy. The amygdala was traced as the entire ovoid gray mass in the medial temporal lobe, bounded by the white matter of the parahippocampal gyrus and the mesial surface of the temporal lobe. Cortex of the uncus (including the gyrus ambiens and the semilunar gyrus) was undoubtedly included in the amygdala ROIs on some slices, because it is impossible to distinguish from the nuclei of the amygdala in coronal MR images.

All regions were traced by one of the authors (TWB or JSA). In a reliability study (two raters, 59 normal subjects) conducted in our laboratory with these criteria for tracing the amygdala and hippocampus, interrater Pearson correlation coefficients (r) were .917 for the left amygdala, .952 for the right amygdala, .93 for the left hippocampus, and .946 for the right hippocampus.

Cortisol Assays

Samples were stored at -20°C until assayed. Salivary cortisol was measured with a commercial immunoassay kit with chemiluminescence detection (CLIA; IBL Hamburg, Germany). Intra-assay and interassay coefficients of variation were less than 10%.

Statistical Analysis

For analysis of the diurnal pattern of cortisol among the groups we used a 5-group (bilateral HC, unilateral HC, BDC, caregiver, healthy comparison) \times 7-sample (awakening, 30 min after awakening, 8:00 AM, 11:00 AM, 3:00 PM, 6:00 PM, and bedtime) multivariate analysis of variance (MANOVA) with repeated measures on the sample factor to test for group differences in level and pattern of cortisol secretion. Owing to the likely violation of the sphericity assumption in repeated-measures designs, MANOVAs were used, as suggested by Vasey and

Thayer (1987), to avoid the inflated type I error rate associated with the mixed-model univariate ANOVA when the sphericity assumption is not met. Three patients (two unilateral HC and one BDC) were excluded from this analysis because of missing samples; appropriate degrees of freedom are reported for each analysis. Differences in cortisol response to awakening were assessed with a univariate ANOVA on the difference in cortisol level between the sample taken upon awakening and the sample taken 30 min later. Owing to the small sample sizes, an effect size analysis was conducted on the cortisol wake response within each group with Cohen's d and 95% confidence intervals (CIs). Similarly, a univariate ANOVA was used to examine differences in the cortisol area under the curve (AUC). The AUC was computed with the trapezoid formula, as suggested by Pruessner et al (2003). Post hoc analyses were conducted with the Games-Howell multiple comparison procedure for unequal sample sizes and variances (Games and Howell 1976). Measures of effect size are reported with eta-squared (η^2). Because of the unequal distribution of men and women across the groups (see demographics information in Results and Table 1), gender is not included as a factor in these analyses. The volume of both right and left amygdalae and right and left HC were combined for separate measures of total amygdala and total HC volumes for use in the correlation analyses. Correlation analyses among the volume of neural structures, time since lesion onset, and cortisol were conducted with Pearson's correlation coefficient.

Results

Demographic and Neuroanatomical Parameters

Table 1 shows means and standard deviations of demographic and neuroanatomical parameters. There was no significant difference among the groups in age [$F(4,40) = 1.4, p > .2, \eta^2 = .12$]. Across all groups, there was a trend toward an unequal balance of gender [$\chi^2(4) = 7.8, p = .09$].

Among the brain-damaged patients, there was no difference in time since onset of brain injury [$F(2,26) < 1, p > .8, \eta^2 = .02$]. The volumes of both the HC [$F(2,23) = 14.0, p < .0001, \eta^2 = .55$] and the amygdalae [$F(2,23) = 4.5, p = .023, \eta^2 = .28$] were different among the groups; post hoc analysis showed that HC volume in the bilateral group was significantly smaller than in both the unilateral HC group and the BDC group ($p = .05$ and $.0001$, respectively). The bilateral HC group had significantly smaller amygdalae compared with the BDC group ($p < .03$) but not compared with the unilateral group ($p > .2$).

Diurnal Cortisol Secretion

See Figure 1 for graphic representation of the diurnal cortisol pattern of all groups. Analysis of cortisol levels throughout the day indicated that there was no difference in overall cortisol level among the groups: no main effect of group [$F(4,37) < 1, \eta^2 = .07$]. There was, however, a main effect of time, indicating significant diurnal variation in cortisol level throughout the day across all groups [$F(6,32) = 19.8, p < .0001, \eta^2 = .78$]. There was not a significant group \times time interaction [$F(24,140) = 1.4, p = .14, \eta^2 = .2$].

To examine differences in cortisol response to awakening, an analysis of the difference between awakening and 30-min-postwake cortisol levels was conducted. This analysis showed a trend toward a significant difference across groups [$F(4,39) = 2.3, p = .08, \eta^2 = .19$]. Post hoc analysis of these data illustrated that the bilateral HC group showed a significantly reduced response to awakening compared with healthy com-

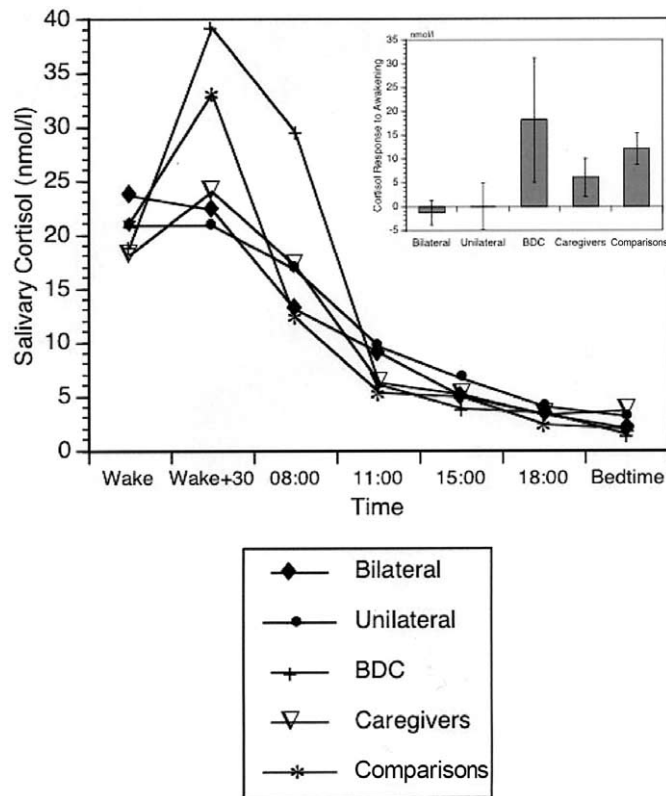


Figure 1. Diurnal cortisol in patients and comparison participants. Data show mean cortisol levels (nmol/L) throughout the day in patients with bilateral or unilateral damage to the hippocampus, brain-damaged comparison patients (BDC), caregivers, and healthy comparison participants. Inset: Mean and SE cortisol response to awakening (sample at 30 min postwake/wake sample) in all groups.

comparison participants ($p = .03$). To examine the effects of differing wake-up times on the cortisol response to awakening, wake-up time was used as a covariate. This variable was not associated with the cortisol response to awakening [$F(1,38) < 1, \eta^2 = .04$].

Within-groups effect size comparison of the wake response indicated that both the healthy comparison participants ($d = .82$, 95% CI $-.12, 1.7$) and the BDC group ($d = .63$, 95% CI $-.57, 1.74$) showed statistically reliable cortisol responses to awakening (although the BDC group showed the largest mean difference, as presented in Figure 1, the variability for this group was very high, resulting in the lower effect size). The caregivers had a smaller effect of awakening: $d = .34$, 95% CI $-.82, 1.45$. Both HC groups showed effect sizes below .1 (95% CI $-.88, .9$). These data indicate that, despite the small sample sizes, HC damage results in a significant reduction in cortisol response to awakening. Additionally, caregivers of these patients show a reduction in the response.

There was no difference in AUC values across the groups [$F(4,37) < 1, \eta^2 = .08$]. Table 1 presents the cortisol AUC values for all participants.

Reliability of Cortisol Diurnal Cycle

For the five patients with HC injury whose salivary cortisol diurnal cycle was tested a second time, there was a strong correlation between the first and second session cortisol AUC values ($r = .7, p = .09$). The cortisol response to awakening was

low on both days (day 1 response = .75 nmol/L, day 2 response = 3.3 nmol/L). Effect size analysis showed that responses on day 1 and day 2 were low effects ($d = .06$ and .3, respectively).

Relationships Between Neuroanatomy and Cortisol

Analysis of the associations between HC volume and cortisol AUC and the cortisol response to awakening revealed no significant correlations. Neither HC volume nor amygdala volume was significantly associated with either cortisol AUC (both $r < |.12|$) or the wake response (both $r < |.07|$). Partial correlation analyses were conducted, controlling for whole brain volume and age. No associations between either HC or amygdala volume and cortisol were found in these analyses (both $r < .05$).

Time Since Lesion and Cortisol Levels

Data from animal research suggest a diminished cortisol level as the time since brain injury increases (Sapolsky et al 1991). We thus calculated the association between the years since brain damage and cortisol AUC and awakening response. There was no relationship among these variables in this patient group (all $r < .08$).

Discussion

Results from this study illustrate that HC damage results in selective alteration of HPA axis function: the cortisol response to awakening was not evident in patients with HC damage. This lack of cortisol response to awakening is documented despite a normal diurnal cycle in patients with both unilateral and bilateral damage to the HC. These results indicate that overt damage to the HC in humans results in altered basal cortisol release that persists into the chronic epoch (>1 year after injury). These results were obtained from patients with damage to the HC from encephalitis, anoxia, stroke, or surgical excision, indicating that this effect is not specific to a particular disease process but to damage to the HC per se. Interestingly, this work replicates a recent study in which a group of six amnesic patients with presumed medial temporal lobe damage, including the HC, failed to show a cortisol response to awakening (Wolf et al 2005).

Although damage to various parts of the human brain have been reported to cause alterations in HPA activity (Feibel et al 1983; Olsson et al 1989; Tchiteya et al 2003), these previous studies were focused on alterations in HPA function immediately after brain damage. Research in both nonhuman primates and rodents has documented a transient glucocorticoid hypersecretion after brain damage—including the HC—that returned to normal with time (Fischette et al 1980; Sapolsky et al 1991). Specifically, Sapolsky et al (1991) demonstrated that hippocampal damage in cynomolgus monkeys resulted in cortisol hypersecretion that was evident at 2 months after brain damage, but the levels had returned to normal by 15 months. Results from the current study show relatively normal absolute cortisol levels in patients with HC damage in the chronic epoch (tested at an average of 6.3 years after brain damage; range, 1–21 years). There was no association between time since HC injury and cortisol level or diurnal pattern, neither in those with overt HC damage nor in brain-injured comparison participants. These findings suggest substantial redundancy in the neural control of HPA axis activity. The primary target of cortisol negative feedback is the paraventricular nucleus of the hypothalamus and the pituitary gland (Dallman et al 1987; Keller-Wood and Dallman 1984; Sullivan and Gratton 2002), although other areas, such as the HC and prefrontal cortex, also play a role in the control of HPA activity (Jacobson and Sapolsky 1991; Sullivan and Gratton

2002). Some of our brain-injured comparison participants showed highly variable cortisol patterns. Future work should address the differential effects of brain damage outside of the HC on HPA activity (see Tchiteya et al 2003).

The HC is necessary for the response of an organism to novelty, both in terms of cognitive detection of novelty (Kishiyama et al 2004) and in terms of corticosteroid response to novel situations (Johnson and Moberg 1980). In fact, it has been proposed that the mineralocorticoid receptors located in the HC are primarily involved in this novelty detection, whereas the glucocorticoid receptors are more involved in consolidation and storage processes of memory (de Kloet et al 1999; Diamond et al 1996; Oitzl and de Kloet 1992). It is possible, therefore, that the cortisol response to awakening is another example of a novelty stress response. This interpretation is certainly supported by anecdotal reports of individuals postponing awakening as long as possible by using the “snooze” button on their alarm clock. Damage to the HC might impair this response, either because of impaired declarative memory of what is to come during the day ahead or mechanisms acting below consciousness and affecting more purely physiologic responses. The fact that several of the patients with unilateral HC damage in the current study show no declarative memory disturbance and no response to awakening suggests a more nonconscious, physiologic explanation for the cortisol response to awakening.

Results from the current study support findings of an association between HC pathology and HPA alterations in humans. Although previous work shows an inverse relationship between HC volume and basal cortisol levels, with HC damage resulting in a transient increase in cortisol (Fendler et al 1961; Sapolsky et al 1991) and chronically elevated cortisol resulting in HC shrinkage, as in Cushing’s disease (Starkman et al 1992, 1999), results from the current experiment did not find such an association in the chronic epoch. This study is among the first, however, to assess basal cortisol release after overt damage to the HC. Wolf and colleagues have recently reported similar findings (lack of morning cortisol response with a normal subsequent diurnal rhythm) from a group of amnesic patients with presumed medial temporal lobe damage (Wolf et al 2005). Previous work has documented alterations in cortisol after HC volume reductions that are due to other disease processes, such as PTSD (Rohleder et al 2004; Yehuda 2001), Alzheimer’s disease (de Leon et al 1988), and Cushing’s disease (Starkman et al 1992, 1999), as well as normal aging (Lupien et al 1998; Wolf et al 2002). Rohleder et al (2004) documented a lack of cortisol response to awakening in PTSD patients; however, PTSD patients also demonstrate a hyposecretion of cortisol throughout the day. Given the association between PTSD and HC volume reductions (Bremner et al 1995; Gilbertson et al 2002), results from these studies suggest that the cortisol response to awakening might be a marker of HC integrity. Future work examining the effects of HC lesions on the cortisol response to stress could address the role of HC integrity in the stress-induced release versus diurnal secretion of this hormone.

The physiologic and psychological significance of the cortisol response to awakening is not well understood (Clow et al 2004). This response to awakening has been demonstrated in all published studies of healthy adults that have assessed this measure, showing an average response of 9.3 ± 3.1 nmol/L across 12 studies (Clow et al 2004). In a study assessing 52 monozygotic twin pairs, Wust et al (2000) demonstrated that the cortisol response to awakening is under significant genetic influence. Environmental influence on the response has been reported as well, including chronic stress (Wust et al 2000), aging (Kudielka and Kirschbaum 2003), and light exposure (Scheer and Buijs 1999). It has been suggested that the

physiologic function of the cortisol response to awakening is in mobilizing energy necessary for the switch from the sleeping to waking hours (Pruessner et al 1997). Researchers have also addressed the role of the response in influencing the immune system (Hucklebridge et al 1998). As previously mentioned, a psychological explanation for the response could be a novelty stress response. Whatever its function, the cortisol response to awakening seems to depend critically on the integrity of medial temporal lobe structures. Future work addressing neural mechanisms of the response is necessary to gain a fuller understanding of its significance.

The caregivers of several of the most profoundly amnesic patients tested in this study showed a reduced cortisol response to awakening. The caregivers’ cortisol response to awakening (difference between awakening level and 30-min-postawakening level: 6.0 nmol/L) was midway between that of bilateral HC patients (−1.3) and normal comparison participants (12.0). Although the stress levels of these participants were not measured, we speculate that these individuals do experience a higher-than-normal stress load because of their role as caregiver. This result is in line with previous work illustrating altered cortisol reactivity in caregivers of chronically ill patients (Da Roza Davis and Cowen 2001; Irwin et al 1997) and a reduced cortisol response to awakening in individuals reporting high levels of social stress (Wust et al 2000). This finding further suggests that the cortisol response to awakening might be a reliable index of an individual’s HPA function (see Pruessner et al 1997; Rohleder et al 2004).

Most studies examining the relationship between the HC and HPA function in humans have focused on the effects of excessive cortisol affecting the HC, but results from this study further illustrate the interactive relationship between the HC and HPA function. Overt damage to the HC results in selective alteration in the function of the HPA axis in the form of abolished cortisol response to awakening. The HC is only one of numerous sites in the brain that exert negative feedback control over the HPA axis, including the hypothalamus, pituitary, and prefrontal cortex (see McEwen 2000 for review). Hippocampal damage alters the dynamics of the control of the HPA axis, resulting in a reduction in the cortisol response to awakening but leaving the remainder of the circadian rhythm intact. Future work could address the time course of the effects of HC damage on cortisol secretion and the possible relationship with memory function.

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