Cortisol responses of healthy volunteers undergoing magnetic resonance imaging

Kevin D. Tessner, *Emory University*
Stephan Hamann, *Emory University*
Karen Hochman, *Emory University*
Elaine Walker, *Emory University*

Journal Title: Human Brain Mapping

Volume: Volume 27, Number 11

Publisher: Wiley | 2006-11-01, Pages 889-895

Type of Work: Article | Final Publisher PDF

Publisher DOI: 10.1002/hbm.20229

Permanent URL: https://pid.emory.edu/ark:/25593/vnnh6

Final published version: http://dx.doi.org/10.1002/hbm.20229

Copyright information:

Cortisol Responses of Healthy Volunteers Undergoing Magnetic Resonance Imaging

Kevin D. Tessner,[1]* Elaine F. Walker,[1] Karen Hochman,[2] and Stephan Hamann[1,3]

[1]*Department of Psychology, Emory University, Atlanta, Georgia*
[2]*Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia*
[3]*Center for Behavioral Neuroscience, Emory University, Atlanta, Georgia*

Abstract: Self-reported anxiety is associated with various medical procedures, including structural and functional magnetic resonance imaging (MRI). The present study tested the hypothesis that MRI scanning would be associated with elevated cortisol levels in participants with no prior scanning experience. Baseline and post-scan cortisol levels, as well as measures of state and trait anxiety, were obtained from scanner-naive (n = 6) and scanner-experienced (n = 8) research participants. The anxiety scores and cortisol responses of the scanner-naive and scanner-experienced participants were compared. Subjects novel to MRI were no more anxious before the scan than were subjects familiar with the MRI examination, but the scanner-naive subjects manifested heightened post-scan cortisol secretion when compared to their pre-scan level and when compared to the scanner-experienced participants. The results are consistent with the hypothesis that the scanning environment can induce cortisol elevations and are congruent with the well-established effects of acute stressors on activity of the hypothalamic-pituitary-adrenal (HPA) axis. The implications for neuroimaging studies are discussed. *Hum Brain Mapp 27:889–895, 2006.*

Key words: MRI; stress; anxiety; cortisol; hypothalamic-pituitary-adrenal; claustrophobia

INTRODUCTION

Subjects undergoing magnetic resonance imaging (MRI) examinations report a number of unpleasant feelings, ranging from claustrophobia (i.e., fear of being closed in or being shut in; fear of suffocation or fear of restriction) to severe anxiety and phobic reactions [Melendez and McCrank, 1993]. These emotional reactions can produce a wide range of complications, such as hyperventilation, accelerated heart rate, sweating, shaking, light-headedness, and nausea, often leading to premature termination of the scan. A review of the literature indicated that between 4% and 30% of patients undergoing MRI experience anxiety-related reactions, ranging from apprehension caused by the confined environment to severe panic that may interfere with the procedure (5%–10%) [Melendez and McCrank, 1993]. About 37% report moderate to high levels of anticipatory anxiety as a consequence of fear of enclosed places (claustrophobia), the possibility of being hurt, fear of the unknown, and concerns about prognosis. Although most participants experience a significant reduction in self-reported anxiety from pre- to post-assessment [Katz et al., 1994], many (30%) report increased feelings of claustrophobia after the scan and approximately one-third are unwilling to undergo another MRI scan [McIsaac et al., 1998].

Dantendorfer et al. [1997] found that pre-scan scores on the Spielberger State-Trait Anxiety Inventory (STAI) were significantly elevated compared to post-imaging STAI

*Correspondence to: Kevin D. Tessner, Emory University Psychological Center, 235 Dental Building, 1462 Clifton Road, Atlanta, GA 30322. E-mail: ktessne@emory.edu

Received for publication 6 May 2005; Accepted 7 November 2005
DOI: 10.1002/hbm.20229
Published online 16 March 2006 in Wiley InterScience (www.interscience.wiley.com).

scores, suggesting that anticipation of the MRI examination increased anxiety levels. Furthermore, patients who developed clinically significant motion artifacts did not show higher pre-scan state anxiety levels; however, patients who reported they were worried about the apparatus before the examination had significantly more motion artifacts [Dantendorfer et al., 1997]. It therefore seems that emotional reactions to the scanner environment can affect the diagnostic utility of MRI. It is thus important to examine the impact of MRI on levels of anxiety, as well as the physiological consequences of the scanner environment.

Given that MRI is stressful for many individuals, it is likely that some also manifest a neuroendocrine response to the experience. In particular, acute physical and psychological stressors have been shown to influence the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis is an important regulatory system that acts through hormone cascades to subserve both behavioral and physiological responses to threat [de Kloet et al., 1998]. Neuroendocrine reactions are an important mechanism used by the body to meet environmental demands and maintain homeostasis [Herman and Cullinan, 1997]. Most noteworthy, activation of the HPA system triggers the release of cortisol, a neurohormone that can alter brain function as indexed by functional MRI (fMRI) [de Leon et al., 1997; Hsu et al., 2003]. To the extent that MRI procedures elevate cortisol, there thus may be concomitant changes in regional patterns of brain activity. To date, we are aware of no published reports on the effects of MRI on cortisol secretion.

A review of the literature on the cortisol response to stressors indicates that most physical and psychological challenges produce heightened salivary cortisol concentrations [Kirschbaum and Hellhammer, 1994]. Tasks that included social-evaluative threat or uncontrollable conditions consistently elevate cortisol levels [Dickerson and Kemeny, 2004]. Furthermore, marked increases in HPA activity have been observed in animals and humans exposed to novel environments [Davis et al., 1999; Hennessy et al., 2000]. In the present study, we measure participants' salivary cortisol before and after fMRI scanning to determine whether fMRI is associated with an increase in cortisol secretion. In addition, we compare the responses of first-time MRI volunteers to those who have undergone previous MRI scanning. Consistent with literature on the effects of acute stressors on cortisol, anticipatory and post-scan increases in cortisol were predicted in subjects naive to the MRI procedure. It was also hypothesized that pre- and post-scan cortisol levels would be higher in scanner-naive volunteers when compared to levels in participants who had undergone MRI 1 week before. The present study also examined the relation between pre-scan anxiety and cortisol. It was hypothesized that an anxiety-provoking situation like the novel scanning environment and the factors identified above (i.e., anticipatory distress, noise, confined spaces, etc.) that are associated with the examination would elevate cortisol levels.

PATIENTS AND METHODS

Participants

Fourteen right-handed young male adults (ages 18–30 years; mean age ± standard deviation [SD], 21.6 ± 3.0 years) underwent two MRI examinations 1 week apart as part of a larger randomized controlled trial investigating the effects of hydrocortisone administration on brain function. Study participants were recruited from the Emory University graduate and undergraduate population. There were seven Caucasian participants, three African-Americans, and four Asians. All subjects were screened for medical disorders by a physician and were found to be physically healthy. None had a history of neurological or psychiatric impairment, learning disability, developmental delay, or previous neuroimaging experience. All were free of medications known to affect HPA system functioning. Our institutional human ethics committee approved the study, and informed consent from each participant was obtained before the first study session.

Study Design

The present study data are from a larger project that involved repeat MRI scans, with placebo and drug conditions administered in a counterbalanced order. A placebo-controlled, double-blind, within-subjects crossover study design was used. Only data from the placebo condition were used for the analysis reported here. All subjects underwent two MRI sessions, and the scanning sessions were scheduled 1 week apart.

Subjects arrived at the General Clinical Research Center (GCRC) of the Emory University Hospital 2 hours before scanning. They had been informed that they would receive either an inert placebo or a drug before undergoing MRI. A licensed nurse checked vital signs (blood pressure, temperature, height, weight, etc.) to establish that they were within normal limits. Oral placebo or hydrocortisone (100 mg) was then administered. Participants who received placebo before the first MRI scan were classified as "scanner-naive" (n = 6), and those who received it before the second scan were designated as "scanner-experienced" (n = 8). The scanner-experienced group thus had been exposed previously to the same scanning procedure 1 week before. (Due to technical problems, data were not available for two participants in the scanner-naive condition.)

As described below, saliva samples were obtained at predetermined intervals beginning 2 hours before the MRI. All MR imaging was conducted on a 3T Siemens whole-body MR system with echo-planar imaging (EPI) upgrade (Siemens, Malvern, PA) and standard headcoil at the Biomedical Imaging Technology Center of the Emory University School of Medicine. Scanning was carried out in a private MRI research suite located adjacent to a larger multipurpose MRI facility in the Emory University Hospital. The MR technician was the same for all participants.

Both structural and functional images were acquired. Scanning sessions lasted approximately 1 hour, and in-

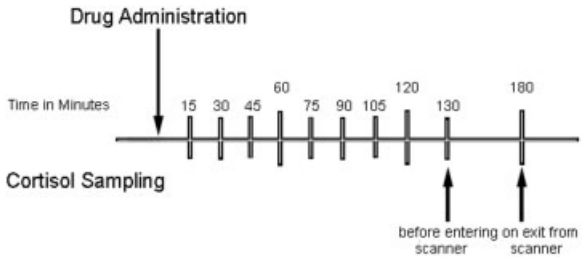

Figure 1.
Saliva samples were obtained every 15 minutes after drug administration until scanning, and at the end of the scanning session.

cluded 6 functional MRI trials (each approximately 5 minutes long) and a 9-minute 3D structural MRI scan using standard gradient recalled echo pulse sequences.

Saliva Sampling

On each visit, a saliva sample was obtained 5 minutes before drug/placebo administration beginning at approximately 10:00 AM (range=8:54 AM to 2:56 PM; mean = 10:17 AM ± 1.9 hours), and a second cortisol sample was taken immediately preceding drug/placebo administration. Participants were then given a 100-mg oral dose of drug/placebo, taken as a pill. Saliva continued to be sampled at regular 15-minute intervals, beginning about 2 hours before entering the scanner. A sample was collected immediately before entering the scanner and immediately after the scanning session for a total of 12 saliva samples. During the period between drug administration and scanning, the same series of cognitive tasks and surveys were completed by the participants in the scanner-naive and scanner-experienced groups. The cognitive tasks performed by each participant were standard verbal and nonverbal memory tasks, similar to those that were subsequently presented in the scanner. These tasks, along with self-report measures of anxiety and personality, were not designed to provoke anxiety.

Self-Reported Anxiety

The State-Trait Anxiety Inventory (STAI, 1983) was administered approximately 1 hour before the time of the scan. This measure is a 40-item questionnaire with well-established reliability and validity [Spielberger, 1983]. Previous research has shown it to be sensitive to anticipatory anxiety associated with MRI scanning [Dantendorfer et al., 1997]. It yields separate scores for state and trait anxiety.

Data Analysis

The final 10 saliva samples obtained from each participant were used to estimate pre- and post-scan neuroendocrine levels. Nine saliva samples were obtained before scanning, and one sample after the MRI. The timeframe for saliva sampling used in the data analysis is depicted in Figure 1. To maximize reliability in the measurement of baseline cortisol, the 9 pre-scan samples were used. To derive an aggregate index of pre-scan cortisol, the average of the first nine samples was computed. The initial two saliva samples were excluded because they were more likely to be indexing reactions to the novelty of the research setting and stress associated with the anticipation of the drug/placebo administration on cortisol levels in the naive subjects. Based on past research [Lacey et al., 2000], these samples were selected to eliminate any anticipatory stress effects of the novel administration of drug/placebo on baseline cortisol levels in the naive subjects. The first saliva sample therefore was collected approximately 15 minutes after the administration of the drug and 2 hours before entering the scanner, with subsequent sampling every 15 minutes. The ninth saliva sample was obtained just before entering the bore of the magnet, and the tenth and final saliva sample was collected as the participant exited the apparatus.

There are normative diurnal changes in cortisol secretion, which entail a decline throughout the course of the day [Weitzman et al., 1971]. To control for variations in time of saliva sampling, residualized cortisol values were derived by conducting regression analyses with time as the independent variable and cortisol values as the dependent variable.

Independent-sample t tests were utilized to compare age, weight, STAI scores, and cortisol values controlled for time of day in the scanner-naive participants with the scanner-experienced volunteers. Statistical tests were two-tailed with $P < 0.05$ considered significant. The statistical design used in this study was a mixed repeated-measures analysis of variance (ANOVA) with group (scanner-naive versus scanner-experienced) as the between-subjects factor and time (pre-scan [mean] and post-scan cortisol values) as the within-subjects factor.

Cortisol Assay

All samples were stored in a −20°C laboratory freezer. Salivary cortisol assays were conducted with the Clinical Assays GammaCoat 125I RIA Kit (DiaSorin, Stillwater, MN). Sensitivity of this kit for salivary cortisol is 0.05 μg/dL and inter- and intra-assay coefficients of variation are 6.0% and 3.5%, respectively.

RESULTS

Statistical analysis revealed no significant differences between the scanner-naive (n = 6) and scanner-experienced groups (n = 8) in age or weight (Table I). Group comparisons showed no differences in state or trait scores from the STAI. Thus, scores on the state index of anxiety were not significantly lower in subjects who had previously experienced an MRI session. It is also noteworthy that the present STAI scores were similar to previously reported norms for young males (35.88 and 35.06 for state and trait STAI scores, respectively). A paired-sample t test indicated that mean pre-scan state STAI scores on the first visit (mean ± SD = 30.13 ± 7.86) were significantly greater than were the mean pre-scan STAI scores the following week (mean ± SD = 25.50 ± 5.63), $t(7) = 2.70$, $P < 0.05$). It was not possible,

TABLE I. Descriptive statistics by group

	Age (yr)	Weight (lbs)	STAI Trait on first visit	Pre-scan STAI State anxiety
Scanner naive (n = 6)	22.8 ± 3.9	162.7 ± 34.4	32.0 ± 5.5[a]	30.2 ± 6.2[a]
Scanner experienced (n = 8)	20.8 ± 1.8	167.9 ± 21.4	28.9 ± 7.9	26.2 ± 7.3[a]
	NS	NS	NS	NS

All values given as mean ± standard deviation. STAI scores were not available for all subjects.
[a] n = 5.
NS, not significant at $P < 0.05$.

however, to ascertain whether these differences reflected anxiety related to the novel procedure or the effects of hydrocortisone administration in those subjects receiving the drug.

Raw cortisol values for the scanner-naive and scanner-experienced group are presented in Table II; however, cortisol values controlled for diurnal variation were used in subsequent analyses. There were no significant differences in baseline index of cortisol levels between the scanner-naive and scanner-experienced subjects. Mixed within-subjects ANOVAs were conducted to test the relation between MRI exposure and cortisol secretion. In the first analysis, the dependent variables were pre-scan (mean) and post-scan cortisol values, the within-subjects factor was time with two levels, and the between-subjects factor was group (scanner-naive vs. scanner-experienced). Mean cortisol (± standard error of the mean [SEM]), by group and time, are illustrated in Figure 2.

The group × time interaction effect was significant ($F[1,12] = 4.833$, $P = 0.048$, partial $\eta^2 = 0.287$. T tests revealed that the scanner-naive subjects had significantly higher post-scan cortisol levels than did the experienced participants ($t[12] = 2.19$, $P = 0.049$). Pre-scan cortisol did not differ by group. Matched sample *t* tests revealed that there were no significant differences between pre- and post-scan cortisol levels for each group.

A second ANOVA was conducted to determine whether there were group differences in the pre-scan cortisol trends. In this within-subjects ANOVA dependent variables were the nine separate pre-scan cortisol values, the within-subjects factor was time, and the between-subjects factor was group (scanner-naive, scanner-experienced). This analysis yielded no significant main or interaction effects.

Correlations between residualized cortisol levels and self-reported anxiety on the STAI before the scan are presented in Table II for the combined sample. The most accurate estimate of the relationship between anxiety levels and cortisol values was computed using the combined sample, rather than the subgroups, given the practical constraints of the small sample size and missing data on the STAI. State anxiety had moderate but nonsignificant correlations with residualized cortisol values pre- and post-scan. The pre-scan state anxiety score was positively correlated with the mean baseline cortisol samples taken within approximately 1 hour before scanning (average of samples 5 to 9) across all subjects.

TABLE II. Descriptive statistics for raw cortisol values and relationships with anxiety

	Scanner-naive (n = 6)		Scanner-experienced (n = 8)		*r* with pre-scan anxiety[a]
Cortisol (μg/dL)	Mean	SD	Mean	SD	
Sample 1	0.49	0.36	0.35	0.11	−0.367
Sample 2	0.40	0.26	0.32	0.10	−0.218
Sample 3	0.44	0.19	0.32	0.11	0.044
Sample 4	0.40	0.13	0.30	0.12	−0.112
Sample 5	0.42	0.08	0.31	0.10	0.460
Sample 6	0.36	0.12	0.32	0.13	0.450
Sample 7	0.32	0.14	0.36	0.15	0.539
Sample 8	0.34	0.16	0.41	0.18	0.506
Sample 9	0.43	0.13	0.33	0.12	0.373
Sample 10	0.52	0.21	0.29	0.10	0.513
Sum of samples 5–9	0.37	0.11	0.35	0.12	0.617[b]

[a] Relationship between STAI state anxiety and residualized cortisol across all subjects.
[b] $P < 0.05$ (one-tailed).

DISCUSSION

The results of this study indicate that individuals undergoing MRI for the first time exhibit increased post-scan

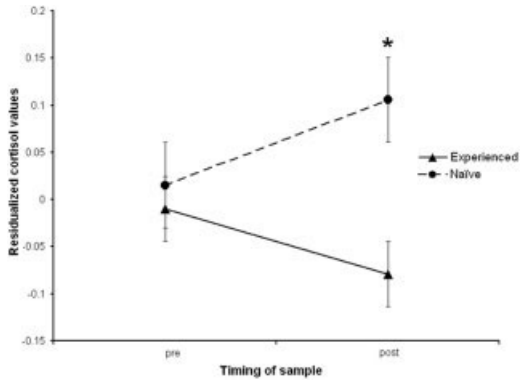

Figure 2.
Cortisol levels at pre- and post-scan (mean ± standard error of the mean) in the scanner-naive and scanner-experienced participants (significant difference between the groups at post-scan: $P < 0.05$).

salivary cortisol levels compared to subjects familiar with the MRI environment and procedure. The present findings are consistent with other studies that have investigated the impact of novel environments and various stress-induction tasks on cortisol levels. The results suggest that MRI can produce an elevation in cortisol like that induced by stressful situations.

Some of the factors in the MRI environment that may lead to stress and post-scan elevations in cortisol include machine noise, uncomfortable temperatures in the magnet bore, the confined space and inability to shift positions during the procedure. Katz et al. [1994] suggest that anticipatory anxiety in patients undergoing MRI stems from fear of the unknown and apprehension about what the test might reveal. Because the imaging carried out for this study was for research purposes, concerns about diagnostic findings would be expected to be minimal. Physical discomfort associated with MRI therefore is the most plausible source of the post-scan cortisol elevations in scanner-naive participants.

The results presented here suggest that pre-scan anxiety levels were not significantly different between first-time MRI participants. Further, mean state anxiety scores for both groups were within normal ranges for individuals of similar ages. These findings are consistent with Katz et al. [1994] who did not identify significant differences in self-report or observer ratings of anxiety between scanner-naive and experienced MRI participants. This may indicate that self-report anxiety measures are insensitive to anticipatory distress, or that individuals who volunteer for fMRI are less inclined to report stress. It may be that the absence of significant group differences in state measures on the STAI is attributable to small sample size.

The loud machine noise and confined atmosphere in the magnet bore may elicit unpleasant anxiety reactions leading to heightened activity of the HPA axis. For example, both acute and repeated noise exposures have been found to activate adrenal hormone secretion in animals, and habituation is reflected in the return to baseline levels after multiple days of treatment [Irwin et al., 1989]. Moelker and Pattynama [2003] have highlighted acoustic noise concerns in fMRI. For example, MR-related acoustic noise has been described to interfere with functional MR acquisition in both direct and indirect ways, such as the noise itself directly increasing blood flow in auditory regions of the brain or the indirect effect of scanner noise on attentional mechanisms leading to cerebral blood flow changes in attention-related cortices [Moelker and Pattynama, 2003].

A meta-analysis investigating acute effects of various types of stressors on humans, however, revealed that noise exposure failed to elicit a significant cortisol response [Dickerson and Kemeny, 2004]. Factors other than the machine noise therefore may be inducing elevations in cortisol levels. Future studies will be needed to identify the components of the MRI procedure that heighten cortisol levels.

Heightened cortisol during MRI is of significant concern to researchers because it has the potential to alter both cognitive functions and brain activity. Studies investigating the effects of cortisol administration on human cognition find effects on cognitive performance, as well as alterations in neural activity. For instance, brief acute periods of cortisol administration or stress exposure can have consequences for memory, as well as executive functions, attention, spatial learning, and emotional processing. Newcomer et al. [1999] conducted a randomized, double-blind, placebo-controlled comparison of several doses of cortisol administered to healthy subjects and found that cortisol treatment at higher doses produced decreases in verbal declarative memory. It seems, however, that moderate concentrations of cortisol are necessary for optimal memory consolidation and retrieval [de Quervain et al., 1998], attention [Lupien et al., 1999], and long term potentiation [Erickson et al., 2003]. Acute cortisol effects in the cognitive domain thus seem to follow an inverted U-shaped curve, with performance deficits at both low and high levels of cortisol concentration [Lupien and McEwen, 1997]. Investigators studying cognitive function using MRI therefore are advised to consider the potential cortisol-mediated effects of the scanning on task performance.

MRI-induced cortisol increases may also have implications for the interpretation of activation patterns associated with the functional mapping of human brain. Experimental studies of the effects of acute cortisol administration suggest that it can alter patterns of neural activity. De Leon et al. [1997] injected elderly subjects with low doses of cortisol (30 mg) and found a generalized reduction in brain activity, especially in the hippocampus. Furthermore, by simultaneously measuring event-related potentials and behavioral performance, Monk and Nelson [2002] found that cortisol administration altered hippocampal activity (in particular, the P600 component, an electrophysiological index of hippocampal activity) and impaired memory performance on tasks of explicit memory. Finally, a recent study by Hsu et al. [2003] revealed that acute administration of cortisol (100 mg) led to a change in the activity of the anterior cingulate cortex of the anterior attention network, leading to a decline in performance on an error-processing task. These results suggest that cortisol can impair performance on tasks that tap executive processes, which may reflect a change in anterior cingulate cortex activity.

Researchers utilizing neuroimaging techniques may begin to consider approaches for dealing with cortisol-related effects of the scanning environment on cognitive performance and brain function. For instance, adequate measurement of neuroendocrine levels and autonomic functioning indices like pulse rates, blood pressure, and skin conductance might be incorporated into imaging studies. Thereby, pre- to post-scan percent changes in biological factors may be used as covariates in the analysis of functional imaging data. Self-reported levels of perceived stress and anxiety might also be considered as factors that may interact with the novel scanning environment to produce alterations in cognitive performance and neural activation. Statistical control for these measures is an approach that may be used in the analysis of brain imaging data.

In interpreting the results of the present study, several limitations should be taken into consideration. First, we do not know the time course of the post-scan cortisol elevation manifested by the scanner-naive participants. No samples were obtained during the 1-hour scan. Previous research indicates that cortisol peaks about 20 to 40 minutes after the onset of stress exposure, and heightened cortisol levels can be sustained for at least 60 minutes after the cessation of stress [Kirschbaum and Hellhammer, 1994]. It is possible that the post-scan elevation partially reflects anticipatory anxiety, but given the absence of any elevation in the hour before the scan, it is more plausible that it is largely a reaction to the MRI experience. Whatever the determinants, the scanner-naive participants did have significantly higher cortisol during some portion of the fMRI. Second, experienced participants in the present study had received a cortisol-inducing drug before their first scan. This may have altered their cortisol response to the second scan, although it does not seem likely that it would have produced the lower post-scan cortisol level observed here.

CONCLUSION

In summary, the present findings indicate that heightened cortisol can result from first time exposure to the MRI scanner. This is important, because it may lead to changes in cortical activity that, in turn, affects cognitive performance in humans. Further studies are needed that include larger numbers of participants to determine the impact that heightened hormone levels in response to the novel scanning environment may have on brain function. In the meantime, serious consideration should be given to stress reduction in research participants undergoing MRI to eliminate the possible cortisol-related confounds.

In addition, for clinical populations including individuals with physical and mental illnesses, one may anticipate that their apprehension and response to the scanner environment may be magnified. Individuals with schizophrenia and depression have been shown to have elevated cortisol levels [Steckler et al., 1999] and tend to be more sensitive to stressful experiences including life events, daily hassles, and acute stress [Walker and Diforio, 1997]. Heightened cortisol levels as a result of pathology or individual differences in reactivity to the scanner environment may confound the analysis of functional imaging data and impact comparative interpretations between groups of participants. Investigators who work with children frequently have used mock scanners to enhance cooperation and reduce anxiety about the procedures. It may be reasonable to consider extending this approach to adults, especially those populations that are more prone to stress reactions. The use of mock scanning procedures may be considered for seriously disturbed subjects to facilitate habituation to the scanner environment. Additionally, neuroimaging studies of patient populations that incorporate neuroendocrine measures will be important to evaluate the effects of the scanner environment on baseline and post-scan cortisol levels. Further research on the relation between biological indicators of stress and patterns of brain activity is also needed.

REFERENCES

Dantendorfer K, Amering M, Bankier A, Helbich T, Prayer D, Youssefzadeh S, Alexandrowicz R, Imhof H, Katschnig H (1997): A study of the effects of patient anxiety, perceptions, and equipment on motion artifacts in magnetic resonance imaging. Magn Reson Imaging 15:301–306.

Davis E, Donzella B, Krueger W, Gunnar M (1999): The start of a new school year: individual differences in salivary cortisol response in relation to child temperament. Dev Psychobiol 35:188–196.

de Kloet E, Vreugdenhil E, Oitzl M, Joels M (1998): Brain corticosteroid receptor balance in health and disease. Endocr Rev 19: 269–301.

de Leon MJ, McRae T, Rusinek H, Convit A, De Santi S, Tarshish C, Golomb J, Volkow N, Daisley K, Orentreich N, McEwen B (1997): Cortisol reduces hippocampal glucose metabolism in normal elderly, but not in Alzheimer's disease. J Clin Endocrinol Metab 82:3251–3259.

de Quervain D, Roozendaal B, McGaugh J (1998): Stress and glucocorticoids impair retrieval of long-term spatial memory. Nature 394:787–790.

Dickerson S, Kemeny M (2004): Acute stressors and cortisol response: a theoretical integration and synthesis of laboratory research. Psychol Bull 130:355–391.

Erickson K, Drevets W, Schulkin J (2003): Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states. Neurosci Biobehav Rev 27:233–246.

Hennessy M, Maken D, Graves F (2000): Consequences of the presence of the mother or unfamiliar adult female on cortisol, ACTH, testosterone, and behavioral responses of periadolescent guinea pigs during exposure to novelty. Psychoneuroendocrinology 25: 619–632.

Herman J, Cullinan W (1997): Neurocircuitry of stress: central control of the hypothlamo-pituitary-adrenocortical axis. Trends Neurosci 20:78–84.

Hsu F, Garside M, Massey A, McAllister-Williams R (2003): Effects of singe dose of cortisol on the neural correlates of episodic memory and error processing in healthy volunteers. Psychopharmacology 167:431–442.

Irwin M, Segal D, Hauger R, Smith T (1989): Individual behavioral and neuroendocrine differences in responsiveness to audiogenic stress. Pharmacol Biochem Behav 32:913–917.

Katz R, Wilson L, Frazer N (1994): Anxiety and its determinants in patients undergoing magnetic resonance imaging. J Behav Ther Exp Psychiatry 25:131–134.

Kirschbaum C, Hellhammer D (1994): Salivary cortisol in psychoneuroendocrine research: recent developments and applications. Psychoneuroendocrinology 19:313–333.

Lacey K, Zaharia M, Griffiths J, Ravindran A, Merali Z, Anisman H (2000): A prospective study of neuroendocrine and immune alterations associated with the stress of an oral academic examination among graduate students. Psychoneuroendocrinology 25:339–356.

Lupien S, Gillen C, Hauger R (1999): Working memory is more sensitive than declarative memory to the acute effects of corticosteroids: a dose–response study in humans. Behav Neurosci 113:420–430.

Lupien S, McEwen B (1997): The acute effects of corticosteroids on cognition: integration of animal and human model studies. Brain Res Brain Res Rev 24:1–27.

McIsaac H, Thordarson D, Shafran R, Rachman S, Poole G (1998): Claustrophobia and the magnetic resonance imaging procedure. J Behav Med 21:255–268.

Melendez J, McCrank E (1993): Anxiety-related reactions associated with magnetic resonance imaging examinations. JAMA 270:745–747.

Moelker A, Pattynama P (2003): Acoustic noise concerns in functional magnetic resonance imaging. Hum Brain Mapp 20:123–141.

Monk C, Nelson C (2002): The effects of hydrocortisone on cognitive and neural function: a behavioral and event-related potential investigation. Neuropsychopharmacology 26:505–519.

Newcomer J, Selke G, Melson A, Hershey T, Craft S, Richards K, Alderson A (1999): Decreased memory performance in healthy humans induced by stress-level cortisol treatment. Arch Gen Psychiatry 56:527–533.

Spielberger C. 1983. State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press.

Steckler T, Holsboer F, Reul J (1999): Glucocorticoids and depression. Best Pract Res Clin Endocrinol Metab 13:597–614.

Walker E, Diforio D (1997): Schizophrenia: a neural diathesis-stress model. Psychol Rev 104:667–685.

Weitzman E, Fukushima D, Nogeire C, Roffwarg H, Gallagher T, Hellman L (1971): Twenty-four hour pattern of the episodic secretion of cortisol in normal subjects. J Clin Endocrinol Metab 33:14–22.