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Cortisol Differentially Affects Memory in Young and Elderly Men

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Nine young and 11 elderly men participated in this placebo-controlled, double-blind, crossover study (0.5 mg/kg cortisol or intravenous placebo). Participants learned a word list before cortisol administration, and delayed recall was then tested. A 2nd word list was learned and recalled after drug administration. In addition, the Paragraph Recall Test and tests measuring working memory (Digit Span), attention (timed cancellation), and response inhibition (Stroop Color and Word Test) were administered at 2 time points after drug administration. Cortisol reduced recall from the word list learned before treatment in both groups but did not influence recall of the list learned after treatment. In contrast, Digit Span performance was decreased by cortisol in young but not elderly participants. The possibility that differential age-associated brain changes might underlie the present results is discussed.

Studies in rats have established that glucocorticoids (GCs) modulate memory (De Kloet, Oitzl, & Joels, 1999; Lupien & McEwen, 1997; Roozendaal, 2000). GCs have beneficial or detrimental effects on hippocampus-mediated spatial memory depending on the timing of the treatment and the specific type of task used (de Quervain, Roozendaal, & McGaugh, 1998; Diamond, Fleshner, Ingersoll, & Rose, 1996; Diamond, Park, Herman, & Rose, 1999; Roozendaal, 2000; Sandi, Loscertales, & Guaza, 1997).

When given acutely in the human, GCs impair hippocampus-mediated declarative memory and frontal lobe-mediated working memory (Kirschbaum, Wolf, May, Wippich, & Hellhammer, 1996; Lupien, Gillen, & Hauger, 1999; Wolkowitz et al., 1990). These effects also apply when GCs are given over a longer period (4–10 days; Newcomer, Craft, Hershey, Askins, & Bardgett, 1994; Newcomer et al., 1999; Schmidt, Fox, Goldberg, Smith, & Schulkin, 1999; Young, Sahakian, Robbins, & Cowen, 1999). de Quervain, Roozendaal, Nitsch, McGaugh, and Hock (2000), in comparing the effects of GCs on learning versus recall components, tried to disentangle at what stage in the declarative memory process the effect occurred. They reported that, for a word list learned 24 hr earlier, cortisol administered just before list recall impaired recall, whereas cortisol administration pre- or immediately postlearning had no effects on list recall (de Quervain et al., 2000).

In vitro studies have demonstrated that GCs inhibit glucose transport into neurons (Horner, Packan, & Sapolsky, 1990). The effects of GCs on specific cognitive tasks have led to speculations about the brain structures and the mechanisms responsible for mediating those effects. Neuroimaging techniques allow a more direct assessment of GC action on specific brain structures. Using fluorodeoxyglucose-positron emission tomography (FDG-PET), we demonstrated that cortisol selectively reduces hippocampal glucose uptake in healthy elderly participants (de Leon et al., 1997). Apart from highlighting the site of GC action, this suggested a mechanism for the effects of cortisol on declarative memory, because sufficient glucose metabolism is necessary for neuronal functioning (Gold, 1995).

Aging in both humans and animals is accompanied by increases in basal cortisol levels and reductions in feedback sensitivity of the hypothalamus–pituitary–adrenal (HPA) axis (Sapolsky, 1992; Sapolsky, Krey, & McEwen, 1986; Seeman & Robbins, 1994; Van Cauter, Leproult, & Kupper, 1996). Furthermore, increased GC levels during aging are associated with a worsening of declarative memory and structural hippocampal damage (Issa, Rowe, Gauthier, & Meaney, 1990; Lupien et al., 1994, 1998; Sapolsky et al.,

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1986; Seeman, McEwen, Singer, Albert, & Rowe, 1997). The effects of age-related HPA axis alterations on frontal lobe structures and functions have not yet been studied. The issue of whether aging influences the acute or chronic effects of cortisol on different memory systems also remains unsettled.

The present placebo-controlled double-blind experiment was conducted to address the following questions: Which cognitive domains (attention, working memory, declarative memory) are affected by cortisol? Are learning and recall of declarative material differentially affected by cortisol? Do cortisol effects occur rapidly (within minutes) or are they delayed (within hours)? Is age a factor in the response to cortisol?

Method

Participants were 9 young and 11 elderly men recruited through the Center for Brain Health, Neuroimaging Laboratory of the New York University School of Medicine. The study was approved by the Institutional Review Board of the New York University School of Medicine. All participants gave written informed consent and were compensated for their time. Participants underwent a thorough screening protocol. The psychiatric screening consisted of the National Institute of Mental Health Quick Diagnostic Interview Schedule (Marcus, Robins, & Bucholz, 1998), Global Deterioration Scale (Reisberg, Ferris, de Leon, & Crook, 1982, 1988), Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975), and Hamilton Psychiatric Rating Scale for Depression (Hamilton, 1967). Participants also underwent a neurological and medical evaluation, which included a complete blood analysis after an overnight fast. The neuropsychological screening included parts of the Wechsler Adult Intelligence Scale—Revised, Wechsler Memory Scale, and the Guild Memory Test (Gilbert, 1996; Gilbert, Levee, & Catalano, 1968; Wechsler, 1981, 1987). Participants with Alzheimer's disease or current or past psychiatric, neurological, or endocrine disorders or those currently taking psychoactive medications were excluded. Demographic data are shown in Table 1. The two groups did not differ in years of formal education, MMSE scores, or body mass index (Bray, 1987). The present experiment studied only men because gender might modulate the effects of stress or glucocorticoids on memory functions (e.g., Seeman et al., 1997; Wolf, Kudielka, Hellhammer, Hellhammer, & Kirschbaum, 1998; Wood & Shors, 1998), and it is likely that fluctuating estradiol levels might be responsible for these effects. Accounting for these possible effects would have necessitated increasing the sample size, rendering the study unfeasible. Women should be studied separately to account for potential estradiol effects.

The study was designed as a placebo-controlled, double-blind, crossover study in which, in the first test session, participants randomly received an intravenous injection of either 0.5 mg/kg cortisol (hydrocortisone sodium succinate; Pharmacia and Upjohn, Kalamazoo, MI) or placebo. This was followed by a second test session 7 to 14 days later in which the injection (placebo or hydrocortisone) not given in the first test session was administered. Participants arrived in the laboratory at 8 a.m. after fasting overnight. See Table 2 for a summary and the timing of the procedures. After first learning a 10-item shopping list to criterion (see later discussion), a 20-gauge catheter was placed in each forearm, one of which was used to administer the drug and the other to sample blood. Both sites were kept patent using heparin locks. The lines were placed at 8:30 a.m., 45 min before drug administration to allow sufficient time for endogenous cortisol levels to return to baseline after the stress of catheter insertions. Baseline blood levels were obtained at 15 and 10 min before injection, and then test blood samples were taken at 15, 30, 45, 60, 90, 120, 150, and 180 min postinjection. Six milliliters of blood were collected into chilled EDTA tubes with each blood draw. Blood samples were kept on ice and then spun down in a refrigerated centrifuge. Serum was separated into aliquots and kept frozen at −70°C until assayed.

Table 1
Demographic Data

	Young (n = 9)		Elderly (n = 11)		
Variable	$M \pm SEM$	Range	$M \pm SEM$	Range	p
Age (years)	24.0 ± 1.2	19–30	69.0 ± 1.8	59–76	<.001
Education (years)	15.5 ± 0.9	11–20	15.8 ± 0.6	12–18	*ns*
MMSE	29.6 ± 0.3	28–30	28.9 ± 0.4	26–30	*ns*
BMI (kg/m^2)	26.0 ± 1.0	21.6–31.7	25.6 ± 1.3	21.0–35.2	*ns*

Note. MMSE = Mini-Mental State Examination; BMI = body mass index.

Hormone Assays

Total blood serum cortisol was measured with a commercial radioimmunoassay (IBL, Hamburg, Germany). This assay has inter- and intra-assay coefficients of variance below 10%.

Cognitive Tests

Several cognitive tests were administered twice during each experimental session (see experimental protocol in Table 2 for details of the timing of pre- and postinjection test administration). Different versions of each test were used for the two sessions. Researchers administering and scoring the cognitive tests were unaware of participants' treatment.

Shopping list. Ten words from a shopping list containing grocery items were presented on a computer screen at a rate of one word every 2 s. After administration of the list, immediate free recall of the list was tested. Participants were selectively reminded of missed items (Buschke, 1973; McCarthy, Ferris, Clark, & Crook, 1981). To ensure uniformity of learning across participants and sessions, a criterion approach was used in which individuals needed to recall the same 8 of 10 words twice. Delayed free recall of the list was tested after 2 hr. Two different lists were used during each session. The timing of the learning and recall of the lists were designed to differentiate the effects of cortisol on recall (first word list) from those on learning (second word list). See experimental protocol (see Table 2). The first list, which was learned (at 8:10 a.m.) before cortisol administration (at 9:30 a.m.), was recalled (at 10:10 a.m.). This allowed the assessment of the effects of cortisol on recall. The second list was learned (at 10:25 a.m.) 1 hr after drug injection and was recalled at 12:25 p.m., thereby allowing assessment of cortisol effects on learning as well as effects on the recall of material learned while cortisol levels were high. The number of trials needed to achieve criterion was used as a measure of learning. The recall performance was evaluated by comparing the performance in the criterion trial with that during the delayed recall performance. Moreover, the number of intrusions during delayed recall was also evaluated.

Paragraph Recall Test. Wechsler-like short stories, each containing 44 content words, were presented to the participants by headphones. We used the same paragraphs that have been used by Craft and Newcomer in several studies investigating the cognitive effect of glucose, insulin, or GCs (e.g., Craft et al., 2000; Newcomer et al., 1999). Two different paragraphs were administered at each session. Immediate and 10-min delayed free recall were recorded on audiotape. The answers were then transcribed and scored by a trained rater, who was unaware of the participants' treatment. The number of recalled content words was used. See the experimental protocol in Table 2.

Stroop Color and Word Test. This test quantifies the ability to inhibit responses by measuring interference caused by the conflict that arises when the participant has to name the color of a printed color word, which is

Table 2
Experimental Protocol Indicating Time of Cognitive Testing and Blood Sampling

Procedure	Time	Cognitive measure
Participants arrive	8:00 a.m.	
	8:15 a.m.	First word list (learning phase)
IV insertion	8:30 a.m.	
Blood sample	9:15 a.m.	
Blood sample	9:20 a.m.	
Cortisol or placebo injection	9:30 a.m.	
Blood sample	9:45 a.m.	First paragraph (immediate recall) Stroop Color and Word Test First paragraph (delayed recall)
Blood sample	10:00 a.m.	Attention test Digit Span First word list (delayed recall)
Blood sample	10:15 a.m.	Profile of Mood States questionnaire Second word list (learning phase)
Blood sample	10:30 a.m.	
Blood sample	11:00 a.m.	
Blood sample	11:30 a.m.	
Blood sample	12:00 p.m.	Second paragraph (immediate recall) Stroop Color and Word Test Second paragraph (delayed recall)
	12:15 p.m.	Attention test Digit Span Second word list (delayed recall)
Blood sample	12:30 p.m.	
End of experiment	12:35 p.m.	

Note. IV = intravenous.

different from the content of the word (e.g., *red* printed in blue letters). Two control conditions (reading only and naming colors only) allow the computation of an interference score (Stroop, 1935). In the version used in this study, participants read or named as many words as possible during a trial of 45 s for each of the three cards. An interference score is calculated using the difference between predicted and actual performance on the third card, as described by Golden (1978). The stronger the interference, the more negative is the interference score. The task was administered twice during the course of the experiment. See the experimental protocol in Table 2.

Attention. A timed cancellation task was used to assess attention. Participants were asked to cross out, on a piece of paper, target items (a three-letter syllable) out of an array of 10 distractors (slightly different three-letter syllables). Number of errors (omissions and false-positive responses combined) and time needed to complete the task were assessed (Convit, Volavka, Czobor, de Asis, & Evangelista, 1994). Selecting different target items, the task was administered twice during the course of the experiment. See the experimental protocol in Table 2.

Digit Span Test. A series of numbers of increasing length were read to each participant at the rate of one digit per second. The participant had to repeat the numbers in the same order (forward condition) or in reverse order (backward condition). Each set length was tested twice. If the participant correctly repeated one set of numbers, the next longer set was administered until he failed a given set length twice, whereupon the task was terminated. One point was given for each correctly repeated digit set, and the scores for the forward and backward conditions were combined, as suggested by Wechsler (1981). The maximum score was 28. This task was administered twice during the course of the experiment. See the experimental protocol in Table 2.

Profile of Mood States. Some previous studies reported effects of cortisol or prednisone on mood (Plihal, Krug, Pietrowsky, Fehm, & Born, 1996; Schmidt et al., 1999; Wolkowitz & Reus, 1999). Therefore, the Profile of Mood States (POMS) was used to control for possible indirect effects of cortisol on cognition mediated by mood changes (see Hertel & Hardin, 1990). The POMS consists of an adjective checklist measuring mood on six different scales (tension, depression, anger, vigor, fatigue, and confusion; McNair, Lorr, & Droppelman, 1992). See the experimental protocol in Table 2.

Statistical Analysis

Data were analyzed with analyses of variance (ANOVAs), with age as a grouping factor (young vs. old) and placebo versus cortisol administration as the within-subject factor. For those tests, which were given twice after drug administration, an additional within-subject factor, time, was included. Tests using different recall conditions (immediate and delayed recall of the word list or immediate and delayed recall of the paragraphs) were analyzed with an additional within-subject factor. This procedure was chosen to minimize the amount of statistical comparisons. Post hoc testing of significant results was performed with Newman–Keuls tests. In addition, for significant ANOVA effects relevant for the present article, the effect size f^2 and ω^2 were calculated (Cohen, 1988; Richardson, 1996; Stevens, 1992). The index ω^2 provides information about the proportion of variance in the dependent variable that is explained by the independent variable. An effect explaining only 1% of the variance is considered small, an effect explaining 6% of the variance medium, and an effect explaining 14% of the variance large (Cohen, 1988; Richardson, 1996; Stevens, 1992).

Results

Cortisol

Hydrocortisone administration significantly increased total serum cortisol levels both in terms of a significant cortisol main effect, $F(1, 18) = 295.03$, $p < .01$, and a significant Cortisol × Time interaction, $F(9, 162) = 82.83$, $p < .01$. Relative to baseline, cortisol levels were significantly elevated 15 min after hydrocortisone injection and declined thereafter ($p < .05$) but were significantly elevated from placebo levels during the entire course of the experiment ($p < .05$). There was no significant difference between young and elderly participants in either baseline or hydrocortisone-induced cortisol levels ($p > .10$). When cortisol levels on the placebo day were analyzed separately with an ANOVA, a significant time effect was observed, $F(9, 162) = 9.00$, $p < .01$, demonstrating the known decline of cortisol levels during the day (see Figure 1).

Cognitive Data

The results for both age groups and each study condition are presented in Table 3.

Declarative memory tests. On the first word list before drug administration, young participants needed significantly fewer trials to reach criterion than the elderly, $F(1, 18) = 12.20$, $p < .01$. There was no significant difference in the amount of trials needed to reach criterion before placebo or cortisol administration (no significant cortisol day main effect or Cortisol Day × Age interaction), $F(1, 18) = 1.74$, $p = .10$, for both effects. However, elderly participants tended to need fewer trials on the cortisol versus the placebo day, reflecting by chance baseline differences (see Table 3 and the following analysis).

Cortisol administration led to a reduced recall of items that were learned before the injection, as seen by a Cortisol × Recall

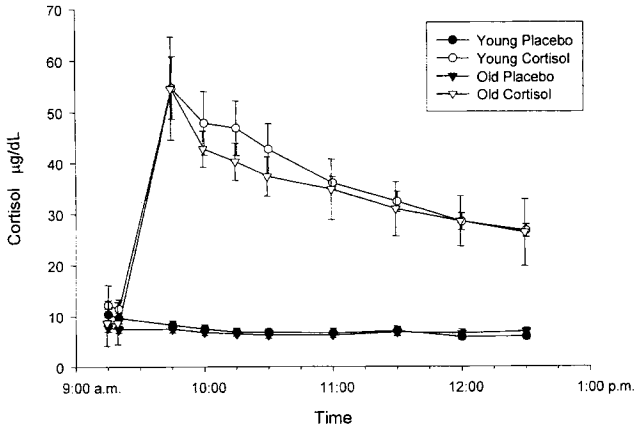

Figure 1. Mean (± *SEM*) plasma cortisol levels in young and elderly participants after administration of 0.5 mg/kg hydrocortisone.

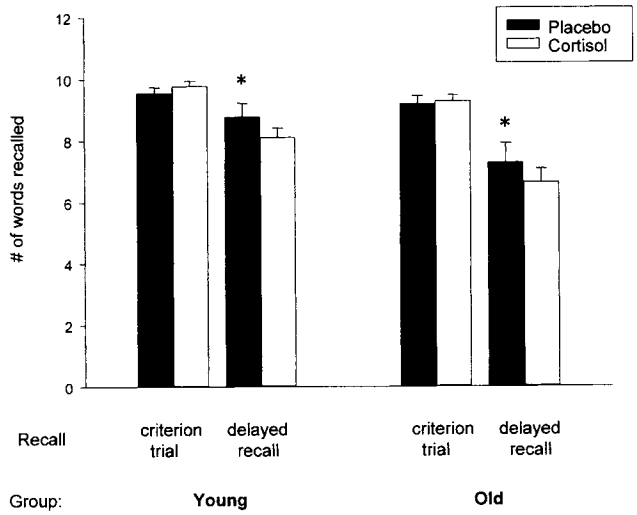

Figure 2. Mean (± *SEM*) effects of cortisol on recall of previously learned words. The 10-item word list was learned 75 min before cortisol administration. Asterisk indicates significant differences between placebo and cortisol group, $p < .05$.

interaction, $F(1, 18) = 8.01$, $p < .05$. There was no Age × Cortisol interaction or Age × Cortisol × Recall interaction (all $ps > .20$; see Figure 2). Post hoc testing revealed that delayed recall was significantly poorer after cortisol administration in both the young and elderly groups ($p < .05$ for both post hoc tests). The effect size f^2 was .088 and ω^2 was .08, indicating that 8% of the variance in the dependent variable was explained by the interaction between cortisol and recall. A ω^2 of .08 is considered to be a medium to large effect size (Cohen, 1988; Richardson, 1996; Stevens, 1992).

Because there was a trend for elderly participants to need fewer trials to reach criterion on the morning before cortisol administration (reflecting by chance baseline differences), we performed an additional analysis of covariance (ANCOVA) to ascertain whether these chance differences during the learning phase could account

Table 3
Cognitive Test Results in Young and Elderly Participants Receiving Cortisol or Placebo

	Young		Elderly	
Test	Placebo	Cortisol	Placebo	Cortisol
Word List 1				
Trials to criterion	2.3 ± 0.2	2.3 ± 0.2	6.2 ± 1.0	4.6 ± 0.7
Recall at criterion trial	9.6 ± 0.2	9.8 ± 0.2	9.2 ± 0.3	9.3 ± 0.2
Delayed recall	8.8 ± 0.4	8.1 ± 0.3	7.3 ± 0.6	6.6 ± 0.4
Intrusions	0.1 ± 0.1	0.0 ± 0.0	0.5 ± 0.3	0.0 ± 0.0
Word List 2				
Trials to criterion	2.8 ± 0.4	2.1 ± 0.1	6.7 ± 0.8	6.5 ± 0.9
Recall at criterion trial	9.7 ± 0.2	9.6 ± 0.2	9.2 ± 0.2	8.9 ± 0.3
Delayed recall	6.5 ± 0.6	6.9 ± 0.9	6.2 ± 0.6	5.7 ± 0.7
Intrusions	1.7 ± 0.7	1.4 ± 0.6	1.1 ± 0.3	1.8 ± 0.6
Paragraph Recall Test 1				
Immediate recall	25.1 ± 1.9	27.1 ± 2.9	21.3 ± 1.5	21.4 ± 1.4
Delayed recall	21.7 ± 2.2	25.0 ± 2.4	19.0 ± 1.8	18.4 ± 1.5
Paragraph Recall Test 2				
Immediate recall	25.1 ± 2.5	24.5 ± 2.8	22.5 ± 1.6	20.4 ± 1.8
Delayed recall	24.1 ± 2.2	23.7 ± 2.9	19.1 ± 1.4	20.1 ± 1.6
Attention Test 1				
Time needed	38.1 ± 2.8	36.4 ± 1.2	50.7 ± 3.0	48.2 ± 2.7
Errors	1.2 ± 0.4	0.8 ± 0.3	1.3 ± 0.4	0.5 ± 0.2
Attention Test 2				
Time needed	35.7 ± 2.3	35.8 ± 1.7	47.5 ± 3.6	49.0 ± 3.2
Errors	1.1 ± 0.4	0.7 ± 0.2	0.9 ± 0.3	1.4 ± 0.3
Stroop 1	4.4 ± 3.6	4.7 ± 3.2	−1.2 ± 2.1	−1.3 ± 1.4
Stroop 2	9.3 ± 2.4	9.3 ± 2.3	−1.3 ± 1.7	2.0 ± 1.4

Note. Values represent means (± *SEM*). Stroop = Stroop Color and Word Test.

for the observed effects on recall. However, when the number of trials needed to reach criterion was entered as a covariate in an ANCOVA model with the same three factors (age, drug, and recall), almost identical results for the Cortisol × Recall interaction were obtained, $F(1, 16) = 10.01$, $p < .05$. Young participants recalled more words than the elderly during both sessions, main effect of age $F(1, 18) = 6.37$, $p < .05$; Age × Recall interaction, $F(1, 18) = 4.23$, $p = .05$. No drug effect on the amount of intrusions was detected ($p > .10$ for main effect and interaction).

The delayed-recall results were also analyzed using change scores (deltas or percentages). A nearly identical significant cortisol effect on delayed recall was observed using these two other ways of analyzing the word list results.

In addition to the group comparison analyses just described, we also evaluated at a descriptive level whether the observed significant effect could have been driven by some outliers. This was not the case. Eleven participants performed poorer under cortisol, whereas only 4 performed better; the remaining 5 performed identically at both sessions.

For the second word list after drug administration, young participants again learned with fewer trials than the elderly, $F(1, 18) = 22.20$, $p < .01$. However, no drug main effect or Drug × Age interaction was observed (both $ps > .10$).

Regarding list recall 3 hr after cortisol or placebo administration, there was no significant drug main effect, Drug × Recall interaction, or Age × Drug × Recall interaction (all $ps > .20$). No drug effect was detected on the amount of intrusions (main effect or interaction; $p > .10$).

To investigate whether recall of the second list was in general poorer, an additional ANOVA was performed with age as the between-group factor and drug (cortisol vs. placebo), list (first vs. second), and recall (immediate vs. delayed) as the within-group factors. This analysis revealed a significant main effect of list, $F(1, 18) = 23.70$, $p < .01$, as well as a significant List × Recall interaction, $F(1, 18) = 10.50$, $p < .01$. Post hoc testing revealed that young and elderly participants showed poorer ($p < .05$) delayed recall on the second list compared with the first list. The effect size f^2 was .12; thus, ω^2 was .10, indicating that 10% of the variance in the dependent variable was explained by the interaction of the two independent variables list and recall. Such an effect is considered to be medium to large (Cohen, 1988; Richardson, 1996; Stevens, 1992). The three-way interaction (Drug × List × Recall) was not significant, $F(1, 18) = 2.80$, $p = .11$, thereby demonstrating that the list order effect was larger than the drug effect.

A similar three-way ANOVA (Age × Drug × List) was performed for trials needed to reach criterion for the list learning. Significant main effects of age, $F(1, 18) = 18.90$, $p < .01$, and list, $F(1, 18) = 5.30$, $p < .05$, were observed. In addition, there was a trend for an Age × List interaction, $F(1, 18) = 3.70$, $p = .07$. Elderly participants tended to need more trials on the second list. The three-way interaction (Age × List × Drug) was not significant, $F(1, 18) = 2.60$, $p = .12$.

Regarding the Paragraph Recall Test, elderly participants tended to recall fewer content words, $F(1, 18) = 3.90$, $p = .06$. However, no cortisol main effect or Cortisol × Age interaction was observed in this test (all $ps > .10$).

Other cognitive tests. On the Digit Span Test, there was a main effect of cortisol, $F(1, 18) = 5.05$, $p < .05$, and also a significant Age × Cortisol interaction, $F(1, 18) = 6.08$, $p < .05$. Young participants performed significantly worse after cortisol administration ($p < .05$), whereas elderly participants did not ($p > .20$). No cortisol interaction with time was observed ($p > .20$). Post hoc testing revealed that under cortisol young participants performed poorer at the second time point ($p < .05$) but not at the earlier time point ($p = .17$; Figure 3). The effect size f^2 was .13; thus, ω^2 was .11, indicating that 11% of the variance in the dependent variable was explained by the Treatment × Age interaction. An effect of such size is considered a medium to large effect (Cohen, 1988; Richardson, 1996; Stevens, 1992). Young individuals tended to perform better than the elderly during both sessions, main effect of age $F(1, 18) = 2.95$, $p = .10$.

When the data were analyzed with the inclusion of recall (forwards vs. backwards) as an additional factor, no significant cortisol interactions with this factor were found (all $ps > .20$).

In addition to the group comparison analysis, we also ascertained at a descriptive level whether the observed significant effect could have been driven by outliers. This was not the case. Eight young participants performed poorer under cortisol, and 1 performed equally at both sessions.

No drug main effects or Drug × Age interactions were observed in the attention test (all $ps > .10$). Elderly participants needed more time to complete the attention task, $F(1, 18) = 11.70$, $p < .01$, but did not differ from the younger men in the number of errors committed ($p > .10$). However, the number of errors committed was in general very low, suggesting a possible floor effect for this variable.

No cortisol effects (main effect or interactions) were observed in the Stroop Color and Word Test ($p > .10$), although elderly participants showed stronger interference, $F(1, 18) = 7.10$, $p < .05$. Similarly, no significant cortisol effects were obtained when the raw test scores (number of words or colors produced for each card) were used instead of the interference score.

Mood. There were no significant changes in self-reported mood scores (POMS) after cortisol administration (cortisol main effect as well as Cortisol × Age interaction; $p > .10$).

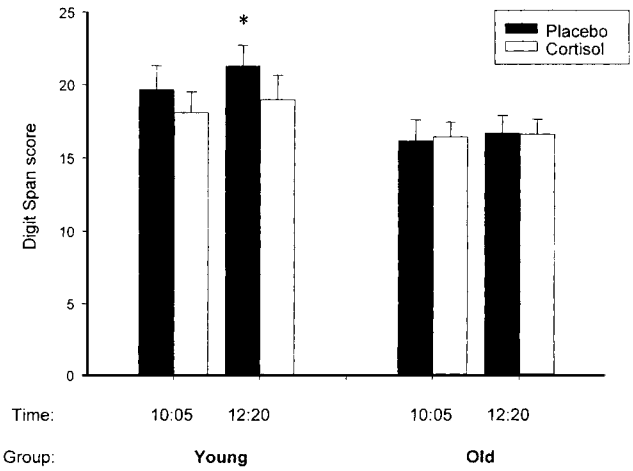

Figure 3. Mean (± *SEM*) effects of cortisol on Digit Span scores in young and elderly participants, measured at two time points after cortisol administration. Asterisk indicates significant difference between placebo and cortisol groups, $p < .05$.

Discussion

The present study has three interesting findings. First, our data demonstrate that cortisol administration impairs recall of word lists learned before drug administration in both young and elderly men. Second, cortisol seems to have no effect on the learning of word lists and paragraphs, nor does it appear to affect delayed recall of word lists and paragraphs learned after cortisol administration. Third, Digit Span is impaired by cortisol administration in young but not elderly participants, whereas attention and response inhibition are not affected in either age group.

Cortisol Effects on the Recall of Declarative Material Learned Before Drug Administration

Our study is unique in showing for the first time that the effects of elevated cortisol levels on free recall of previously learned material appear to be relatively independent of age. Recall of words learned before cortisol administration was impaired after cortisol administration in both young and elderly participants. This is in agreement with studies in young rats and humans in which recall of material learned 24 hr earlier was impaired when GCs were given before delayed-recall testing (de Quervain et al., 1998, 2000). We confirm and extend these findings by showing that recall of material learned 75 min before cortisol administration is also negatively influenced by cortisol. In addition, the results are also in line with the reductions in recall observed after psychosocial stress-induced cortisol elevations (Lupien et al., 1997; Wolf et al., 1998). Our design does not allow us to exclude the possibility that the observed effects were mediated by cortisol effects on consolidation, which is still ongoing 75 min after the initial learning (McGaugh, 2000). However, de Quervain et al.'s (1998, 2000) results suggest that the effects were indeed caused by a specific cortisol effect on recall.

The word list used in the present study was rather short (10 words) and was learned thoroughly to a criterion. Animal data suggest that the effects of GCs (or stress) on memory are larger with increasing task difficulty (Diamond et al., 1999). Therefore, it is likely that the cortisol effect would have been larger had we used more words in the list and the training been less intensive. Indeed, the task used by de Quervain et al. (2000) was more difficult because these investigators used a larger list (60 words), did not train to a criterion, and tested recall after a longer delay (24 hr). This might explain why the cortisol-induced decrease in delayed recall observed by de Quervain et al. was larger than the one observed in the present experiment. However, utilization of this short list still allowed us to detect drug, age, and interference effects. Therefore, even though the actual differences were small, the list used had high sensitivity. Although the absolute reduction in the amount of words recalled was relatively small, the effect size calculation indicated that cortisol administration explained 8% of the observed variance, which reflects a medium to large effect (Cohen, 1988; Richardson, 1996; Stevens, 1992). This effect size could be of clinical relevance in that it may make the difference between getting an A or a B on an examination.

We hypothesize that the negative effects of cortisol on recall are mediated by its effects on the hippocampus. This notion is supported by two lines of evidence. First, functional neuroimaging studies, animal lesion experiments, as well as clinical observations demonstrate that the hippocampus is important for successful memory retrieval (Eichenbaum, Otto, & Cohen, 1992; Lepage, Habib, & Tulving, 1998; Nyberg, McIntosh, Houle, Nilsson, & Tulving, 1996; Schacter & Wagner, 1999; Squire, 1992). Moreover, healthy young and elderly participants seem not to differ in their hippocampal activation during memory retrieval (Schacter, Savage, Alpert, Rauch, & Albert, 1996). The second line of evidence comes from our previous resting FDG-PET study (de Leon et al., 1997), which suggested that a cortisol-induced reduction in hippocampal glucose metabolism may be the mechanism underlying the negative impact of cortisol on retrieval. However, in that study, only elderly individuals were tested; therefore, it remains to be shown whether a similar reduction in hippocampal glucose uptake occurs in young individuals. The role of the hippocampus in mediating the cortisol-induced recall reduction should be investigated in the future using a cortisol challenge during a functional imaging examination of retrieval.

Cortisol Effects on Learning of Declarative Information and Its Subsequent Recall

High cortisol levels seem to have no effect on the learning of new material 1 hr after injection or on the recall of that material 3 hr postinjection. The absence of a cortisol effect on the retrieval of material learned during elevated cortisol levels can be interpreted in at least three ways. The simplest possibility is that cortisol effects do not persist over 3 hr. Although cortisol concentrations significantly declined during the course of the experiment, they were still significantly elevated 3 hr after administration (as shown in Figure 2). Moreover, it was during this time that Digit Span was affected. However, it is possible that different brain structures (hippocampus vs. frontal lobes) have different cortisol response profiles. A second explanation invokes the concept of state-dependent learning (Bustamante, Jordan, Vila, Gonzalez, & Insua, 1970; Gray, 1975; Reus, Weingartner, & Post, 1979; Stewart, Krebs, & Kaczender, 1967). The recall of material learned under normal cortisol levels is impaired by high cortisol levels, but the recall of material learned while cortisol levels are high may not be influenced by high cortisol levels. Future studies using a design similar to that of de Quervain et al. (2000) could test this hypothesis by giving cortisol before learning and before recall testing and contrasting the results with the observed adverse effects achieved when cortisol is given before recall testing only. It is also possible that the effect of cortisol on material learned during high cortisol was masked by nonspecific effects inherent in our design. For example, we observed that the delayed recall of the second word list was in general poorer than that of the first list. The size of the negative effect of the repeated list presentation (comparison of the first and second lists, irrespective of treatment) was larger than that of the cortisol administration (comparison of recall of the first list under cortisol vs. placebo). This decreased performance could be reflective of rather nonspecific changes during the long experimental session (e.g., increased fatigue) or of proactive interference from previously learned material. Because participants under cortisol recalled fewer items from the first list, the amount of proactive interference could have been reduced, thereby masking a possible negative effect of cortisol on recall of the second list. Preliminary experimental evidence, that cortisol might reduce the

amount of proactive interference, has been presented (Watson, Baker, Astana, Peskind, & Craft, 2000).

Learning and recall of paragraphs also were not impaired after cortisol treatment. State-dependent learning, mentioned previously, could also be used to explain the absence of a deleterious effect on Paragraph Recall. However, other explanations are possible. The relatively short delay time (10 min) could have decreased the task difficulty and with it its sensitivity. However, our findings are in agreement with some previous studies in which paired associates (Lupien et al., 1999) or Paragraph Recall (Newcomer et al., 1994, 1999) tests were used. One other study observed an increased amount of intrusion after GC administration in a word list paradigm (Wolkowitz et al., 1990). However, this latter study used dexamethasone (DEX) instead of cortisol, perhaps accounting for the observed differences. DEX does not cross the blood-brain barrier as readily as cortisol (see De Kloet, Vreugdenhil, Oitzl, & Joëls, 1998; Miller et al., 1992) and suppresses endogenous cortisol production (Arana, Baldessarini, & Ornsteen, 1985).

In contrast to the absence of an acute cortisol effect on learning, as demonstrated by this study, prolonged experimental GC exposure seems to impair learning of declarative material in animals (Conrad, Galea, Kuroda, & McEwen, 1996; Luine, Villigeas, Martinez, & McEwen, 1994; Ohl & Fuchs, 1998) as well as humans (Newcomer et al., 1994, 1999; Schmidt et al., 1999; Young et al., 1999). In addition, humans exposed to prolonged endogenous high cortisol levels also demonstrate impaired learning (Lupien et al., 1994, 1998; Seeman et al., 1997; Starkman, Gebarski, Berent, & Schteingart, 1992). These observations suggest different underlying mechanisms for the acute and chronic effects of GCs. For reviews on this topic, see McEwen (1997, 1999a, 1999b) and De Kloet et al. (1998).

Cortisol Effects on Digit Span: Evidence for Age Differences

The third and heretofore never reported finding is that cortisol impaired Digit Span performance in young but not elderly individuals. Interestingly, the cortisol effect was more pronounced at the second test point (almost 3 hr after cortisol administration), suggesting involvement of either genomic or indirect effects. One could also speculate that cortisol, in part, reduced the practice effect observed during the placebo session in young individuals rather than impairing the performance directly. The age-related differences in the cortisol effects cannot be explained by simple differences between the groups. The two groups did not differ in the number of years of formal education, MMSE scores, or cortisol levels achieved after cortisol administration. However, it is possible that the baseline differences in test performance between young and elderly individuals altered the sensitivity of the test to detect subtle changes. Although the absolute reduction in performance for Digit Span under cortisol was relatively small, the effect size analysis revealed that 11% of the variance was explained by the experimental condition, which reflects a medium to large effect (Cohen, 1988; Richardson, 1996; Stevens, 1992). When we designed this experiment, we did not anticipate that cortisol would have much of an effect on frontal function; Digit Span was being used as a control task. Therefore, additional studies using more sophisticated working memory tasks are clearly needed to confirm our results. Our finding that cortisol impaired Digit Span performance in young individuals is in line with Lupien et al.'s (1999) study, which found that cortisol among young individuals increased reaction time in the Sternberg paradigm, a measure of "scanning time" in short-term memory (Sternberg, 1966). Another study previously reported that cortisol impaired mental rotation (Kirschbaum et al., 1996), a task also thought to have a working memory component. Short-term memory storage has long been ascribed to the frontal lobes, and functional neuroimaging studies support this notion (Gabrieli, Poldrack, & Desmond, 1998; Smith & Jonides, 1998; Smith, Jonides, Marshuetz, & Koeppe, 1998). For example, a systematic increase in working memory load, similar to that occurring during the Digit Span task, linearly increases activation of the dorsolateral prefrontal cortex (Braver et al., 1997; Cohen et al., 1997; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999). However, the Digit Span Test is not a pure measure of working memory because it also measures attention (see Lezak, 1995). Nonetheless, our findings cannot simply be explained by changes in attention, because we and others did not find cortisol effects on several more direct measures of attention (Lupien et al., 1999; Newcomer et al., 1994, 1999; Schmidt et al., 1999).

The effects of cortisol on the frontal lobes appear to be restricted to the short-term storage of information in working memory. No cortisol effect was observed on the Stroop Color and Word Test, which measures frontal cortex-mediated impulse inhibition. Similarly, Young et al. (1999) found cortisol effects on working memory tasks but not on the Tower of London test, a task measuring logical reasoning. Different structures within the frontal lobe mediate these different tasks (Cohen et al., 1997; Malloy & Richardson, 1994; Smith & Jonides, 1998; R. L. West, 1996), and it is possible that these regions are differentially affected by cortisol. The present study had a relatively small sample size. Therefore, the specificity of the cortisol effects on short-term storage needs to be confirmed in future studies. In addition, there is always the possibility that some of the other tasks used might have been less sensitive to subtle drug-induced changes.

Our findings, if replicated with other working memory tests, suggest that with normal aging the frontal lobes (probably the dorsolateral prefrontal cortex), but not the temporal lobes, may become less responsive to the effects of acute cortisol elevations. We hypothesize that age-related alterations of the frontal cortex may account for this lack of responsivity. Previous studies lend indirect support to this hypothesis. For example, in conditions that affect particular brain anatomy, as in the case of the hippocampus in schizophrenia (Lawrie & Abukmeil, 1998) or Alzheimer's disease (de Leon et al., 1993), the compromised hippocampus is not responsive to cortisol effects on memory (Newcomer et al., 1998) or glucose utilization (de Leon et al., 1997). In contrast to these pathological conditions, it is known that with normal aging substantial changes may occur in the frontal lobes (e.g., Coffey et al., 1992; Coleman & Flood, 1987; De Santi et al., 1995; Haug & Eggers, 1991; Raz et al., 1997; Salmon et al., 1991; R. L. West, 1996), whereas age-associated changes in the medial temporal lobes are more subtle (Coffey et al., 1992; Raz et al., 1997; M. J. West, 1993).

We hypothesize that the lack of frontal lobe sensitivity to the acute effects of cortisol during normal aging could be analogous to the absence of hippocampal cortisol effects in clinical conditions

with hippocampal disease. Age-associated changes in the frontal dopamine system, which is critically involved in working memory (Goldman-Rakic, 1998), may explain some of these age differences. The frontal dopamine system is sensitive to the effects of stress (Deutch & Roth, 1990) or GCs (Piazza & Le Moal, 1996). Arnsten and Goldman-Rakic (1998), in their study of monkeys, demonstrated that stress impaired working memory through a "hyperdopaminergic" mechanism. Because dopamine concentrations and receptors decrease with age (Goldman-Rakic & Brown, 1981; Wenk, Pierce, Struble, Price, & Cork, 1989), elderly individuals may be less susceptible to this effect. Supporting this hypothesis are studies demonstrating age-associated reductions in the sensitivity to dopamine agonists (Arnsten, Cai, Murphy, & Goldman-Rakic, 1994; Arnsten, Cai, Steere, & Goldman-Rakic, 1995).

To our knowledge, this communication represents the first report of an age-associated differential modulation of two distinct effects that acute cortisol elevation has on human cognition. First, cortisol impairs recall of declarative material learned before drug administration, and this effect is observed in both young and elderly individuals. Second, short-term storage or working memory is impaired by cortisol only in young participants. Because only men were studied in this experiment, it awaits to be shown whether similar effects are observed in women. A somewhat speculative explanation for our results is that with normal aging the sensitivity of the frontal cortex to acute cortisol elevations is attenuated, whereas the sensitivity of the hippocampus is not. However, as outlined previously, several other methodological explanations for the present findings are possible and have to be ruled out in future studies. The final test of our hypothesis can only come from functional imaging studies of declarative memory recall and working memory performance after cortisol administration.

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