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ORIGINAL INVESTIGATION

Increased cortisol levels in cognitively challenging situations are beneficial in young but not older subjects

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Abstract
Rationale Adaptation to stressful situations changes with increasing age. This is also reflected in age-related differences in effects of acute stress on, e.g., episodic memory. Less is known about age-related differences of the cognitive effects of individual stress responses to challenging situations.
Objective To investigate the influence of the individual cortisol response (as a marker for the individual stress level) on behavioral and neural measures during a challenging memory paradigm.
Materials and methods Twenty young and 12 older subjects were scanned using functional magnetic resonance imaging during encoding and retrieval of spatial contextual information. Salivary cortisol levels were measured before and after scanning.
Results A multiple regression analysis of behavioral data showed an interaction effect of age and cortisol response on memory for the items and their spatial context during retrieval due to increased accuracy with increasing cortisol responses in young compared to old subjects. During encoding, this was reflected in a positive effect of the cortisol response on prefrontal activity in young but not in older subjects. During retrieval, there was a negative effect of the cortisol response on brain activity in the hippocampus and prefrontal regions in older but not in young subjects.
Conclusions The data suggest an increased efficiency to encode items and their context with increasing cortisol responses in young subjects, and a decreased efficiency to retrieve information with increasing cortisol responses in older subjects. We conclude that neuroendocrine responses are differentially associated with behavioral and neural measures in cognitively challenging situations in young and older volunteers.

Keywords Stress · Cortisol · Episodic memory · Aging · fMRI · Hippocampus

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Introduction

Acute stress exposure elevates cortisol levels and interacts with human cognition. Glucocorticoids, which are released together with catecholamines during stress, can have beneficial as well as detrimental effects on different memory functions in animals and humans (Diamond et al. 2007; Joels et al. 2006; Roozendaal et al. 2006a; Wolf 2008). On the one hand, increased levels of glucocorticoids enhance memory consolidation in rodents (McGaugh and Roozendaal 2002;

Roozendaal 2002) and humans (Abercrombie et al. 2003; Buchanan and Lovallo 2001; Cahill et al. 2003). On the other hand, glucocorticoid administration can impair memory retrieval (de Quervain et al. 1998, 2000, 2003; Het et al. 2005; Roozendaal 2002; Wolf et al. 2001a; Wolf 2003). Furthermore, it has been shown that endogenous glucocorticoid release triggered by experimentally induced acute stress impairs memory retrieval: while some studies have shown significant differences in memory retrieval between stressful and non-stressful conditions (Jelicic et al. 2004; Kuhlmann et al. 2005; Payne et al. 2002), other studies did not show such an effect but nevertheless revealed negative correlations between the cortisol response and memory performance (Kirschbaum et al. 1996; Takahashi et al. 2004; Wolf et al. 2001b).

Cortisol is a corticosteroid hormone released from the adrenal gland. Its production is regulated via the so-called hypothalamo-pituitary-adrenocortical axis. Aging is associated with both a reduced cortisol feedback inhibition via the hypothalamo-pituitary-adrenocortical axis (Li et al. 2006; Otte et al. 2005) and deficits in memory, particularly with regard to spatial or temporal contextual information (source memory; Craik and Jennings 1992; Light 1991; Naveh-Benjamin 2000, 2003, 2004; Spencer and Raz 1995; Tulving 1983). An increasing number of studies have investigated possible interactions of cortisol levels and cognitive decline with aging. Longitudinal studies have shown that increased basal cortisol levels correlate with worse cognitive performance in old subjects (aged ~60 to 80 years; Lupien et al. 1994, 1998). Other studies suggest that there are also age-dependent changes in the reactivity to acute cortisol level increases through pharmacological modulation (Wolf et al. 2001a), as expressed by a negative effect of cortisol on working memory in young but not in older subjects. However, age-related differences in neural correlates of memory functions during cognitively challenging situations have not yet been investigated.

In the present study we investigated the relationship between the individual cortisol response (as a marker for the individual stress level) during a demanding source memory paradigm within a functional magnetic resonance imaging (fMRI) scanner on the one hand and the behavioral performance and memory-related neural activity on the other hand. To investigate age-related changes with respect to the individual stress response and spatial contextual memory, the data were compared between young and older subjects.

Materials and methods

Participants Twenty-two young (12 male, aged 19–29 years, mean age 23.8±2.8 years) and 17 older subjects (8 male, aged 52–71 years, mean age 58.5±5.5 years), all without history of neurological or psychiatric disease, took part in the present study which was part of a larger investigation (Kukolja et al. 2008). All were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield 1971). All subjects were free of medication known to affect the hypothalamo-pituitary-adrenal axis (e.g., antihistaminic or antiserotoninergic drugs, oxytocin or corticosteroids) or cognition and gave informed written consent prior to participation. Ethics approval was obtained from the local ethics committee. All subjects had normal or corrected-to-normal vision. The two groups were matched for level of education. Six (two young, four old) volunteers were excluded due to guessing in the spatial contextual judgments (see below), and one older subject was excluded due to a cortisol response (+42.714 nmol/l) which exceeded the group mean (−0.523±10.003 nmol/l) by more than 3 SDs. Thus, 20 young (11 males) and 12 older subjects (eight males) remained for further analysis.

Task We used a spatial contextual memory task employed previously by Cansino et al. (2002) and Kukolja et al. (2008). The experiment consisted of an encoding and a retrieval session. Color photographs of natural and artificial objects were projected onto a screen in front of the participant in the MRI scanner (viewing distance ~29 cm). The baseline display consisted of a cross dividing the screen into four quadrants. During encoding, 64 of 96 stimuli were selected for each subject. The stimuli appeared randomly for 1,000 ms in one of the four quadrants, followed by an inter-stimulus interval (ISI) of 1,600 ms. Subjects were told to memorize each item *and* its position. Subjects indicated with fingers of their right hand whether the object was "natural," e.g., a vegetable, or "artificial" e.g., a tool.

During retrieval, all 96 (64 old + 32 new) stimuli were presented randomly at the center of the screen. Stimuli were presented for 1,500 ms, followed by a 2,300-ms ISI. The subjects' task was to decide whether each picture was novel or old (i.e., previously presented). If an item was old, subjects had to indicate the position where the stimulus had appeared during encoding via button presses with the right hand (spatial context judgment). The durations of the encoding and retrieval session were 4.7 and 8.7 min, respectively, with a 4-min pause in between. After acquisition of the functional images, a high-resolution T1 anatomical image was obtained for each subject, which lasted for another 10 min. In both sessions, one third of the stimuli were null events which merely showed the baseline picture. Prior to scanning, subjects performed one training session outside and one inside the scanner.

Cortisol analysis Saliva samples were collected immediately before and after scanning (time interval: approximately 40 min) for each subject using Salivette (Sarstedt, Nümbrecht, Germany) collection devices and stored at −20°C until biochemical analysis. Free salivary cortisol

levels were measured at the Institute of Biopsychology, Technical University Dresden, Germany using a commercially available chemiluminescence assay (IBL, Hamburg, Germany). As an indicator for the individual stress response, we used the difference between post- and pre-fMRI salivary cortisol levels (cortisol response) in all further analyses (Kirschbaum et al. 1996; Wolf et al. 2001b). Using this value as a marker for the individual stress response accounts for the interindividual variability in baseline cortisol levels. The additional inclusion of baseline cortisol levels as a nuisance variable into the analyses defined below accounts for any possible confounding effect of the individual baseline cortisol levels.

Behavioral data analysis We focus our data analysis on median reaction times (RTs) and response accuracy for items which were correctly recognized as "old" during retrieval. These were divided into two subtypes: items with a correct spatial context judgment (CorSCR) and items with a false spatial context judgment (FalSCR).

We used a multiple regression analysis to investigate the relation between the individual cortisol response, item and spatial contextual memory, and aging. This approach identifies between-group differences of the association of the cortisol response with spatial contextual memory (i.e., CorSCR number and CorSCR RTs during retrieval) and item memory (i.e., the sum of CorSCR + FalSCR and RTs). The equation was as follows:

$$y=\beta_0+\beta_1*\text{cortisol response}+\beta_2*Y_0O_1 +\beta_3*Y_0O_1*\text{cortisol response}+b_4*\text{time of day} +\beta_5*\text{gender}+\beta_6*\text{pre}-\text{scan salivary cortisol}+\varepsilon$$

where Y_0O_1 was an indicator variable assigning '0' to young and '1' to older subjects, and the third variable was the interaction effect of the cortisol response and the indicator variable (Rawlings et al. 2001). To account for differences in the day time of the testing (which took place between 8 A.M. and 4 P.M.) or gender (Otte et al. 2005; Wolf et al. 2001b), both variables were included as nuisance covariates. Prescan cortisol values were included as a covariate since they were negatively correlated with the cortisol response ($r=-0.640$, $p<0.0001$, $n=32$), which corresponds to previous findings (Dickerson and Kemeny 2004), but may represent a statistical artifact (regression to the mean). Importantly, the inclusion of prescan cortisol values as a covariate assured that the effects observed were exclusively due to cortisol responses. ε was the error term. β_1 provided an estimate for the association of the cortisol response and behavioral markers in young subjects, since the variables two and three were equal to zero. In order to calculate the analogous association in older subjects, we inverted the indicator variable to Y_1O_0 assigning '1' to young and '0' to older subjects.

In order to investigate a possible effect of baseline cortisol levels on behavioral performance, an analogous analysis was performed with prescan cortisol levels.

Neuropsychological data analysis On a separate day all subjects underwent neuropsychological assessment which included the CERAD screening of dementia [containing the MMSE, German version (Kessler et al. 1990)], an assessment of subjective memory complaints [MAC-Q (Crook et al. 1992)], and measures of verbal IQ [MWT-B (Lehrl 1995)], working memory [digit span, HAWIE-R (Tewes 1991)], and word fluency [letters FAS Benton and Hamsher (1976)].

A correlation analysis between the cortisol response and the neuropsychological test data was performed to reveal the influence of the neuropsychological profile on the cortisol response at the time of MR scanning.

FMRI hardware and procedures Functional MR images were acquired using a SONATA 1.5-T whole-body scanner (Siemens, Erlangen, Germany) equipped with a standard head coil. Sequence parameters were: T2*-weighted echoplanar images (EPI) with blood-oxygenation level-dependent (BOLD) contrast, echo time=66 ms, repetition time=3,020 ms, flip angle=90°, slice thickness 4.0 mm, interslice gap 0.4 mm, in-plane resolution=3.125 mm×3.125 mm, and thirty sequentially acquired axial slices per volume. A high-resolution T1 anatomical image was obtained for each subject. The image preprocessing was performed using SPM2 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk). The fMRI time series consisted of 93 images for encoding and 172 images for retrieval. The first five images of each session were discarded until the MR signal reached equilibrium. After realignment and slice time correction, the EPI images were spatially normalized to the EPI template provided by SPM2 (resampled to $3\times3\times3$ mm^3 voxels) (Friston et al. 1995) and smoothed with a Gaussian kernel of 8 mm (full-width-half-maximum).

Statistical analysis was performed using SPM5 employing random effects models. The two sessions (encoding, retrieval) were analyzed separately. For encoding, three event types were defined at the first level: CorSCE, FalSCE, and a regressor including subsequently forgotten items and misses. For retrieval, the model comprised CorSCR, FalSCR, and a regressor including forgotten, new, and missed items. The head movement parameters were included as confounds. Events were modeled as stick functions which were convolved with a canonical hemodynamic response function (HRF) and its first-order temporal derivative. The data were high-pass filtered to 1/128 Hz to remove low frequency drifts. The parameter estimates for the HRF and their linear contrasts comprised the data for the second-level analysis. At the second level, brain activity during encoding and retrieval was correlated with the cortisol response in a multiple regression

approach analogous to the behavioral data analysis. Only activity associated with successful encoding (CorSCE) or retrieval of spatial context (CorSCR) was included in the analysis. The design matrix included six regressors: (1) the cortisol response (orthogonalized to the prescan cortisol values), (2) the indicator regressor Y_0O_1, (3) the interaction of the cortisol response and Y_0O_1, and the nuisance covariates (4) gender, (5) time, and (6) prescan salivary cortisol. Analogous to the analysis of the behavioral data, the third regressor revealed a cortisol response × age interaction, while the first regressor revealed an association of the cortisol response and brain activity in young subjects. In order to investigate the association of the cortisol response on brain activity in older subjects, the indicator regressor was reversed to Y_1O_0. The tests resulted in an *F*-statistic for every voxel. The resulting set of voxel values for each contrast constitutes a statistical parametric map of the *F*-statistic $SPM_{\{F\}}$, which was subsequently transformed to the unit normal distribution $SPM_{\{z\}}$. Activations are reported at $p<0.001$, uncorrected, and >ten contiguous voxels.

The anatomical localization of significant activations was assessed by reference to the Montreal Neurological Institute, Montreal, Canada (MNI) standard stereotactic space which approximates the Talairach system (Talairach and Tournoux 1988).

Results

Cortisol response Salivary cortisol levels (mean and standard error) in young subjects were 12.534±1. 571 nmol/l (range 5.181–29.935) and 10.705±1.491 nmol/l (range 1.236–31.300) before and after the experiment, respectively. In older subjects, the mean salivary cortisol levels before and after the experiment were 9.287±1.116 nmol/l (range: 5.145–18.047) and 10.777±1.593 nmol/l (3.697–31.083), respectively. A repeated-measures ANOVA with the within-subject factor cortisol time (before, after) and the between-subject factor age group neither revealed any effect of age, cortisol time, nor any interaction between age and cortisol time.

In young subjects, the mean salivary cortisol response was −1.829±1.982 nmol/l (range −6.828 to 22.233), while older subjects showed a mean cortisol response of 1.489± 1.639 nmol/l (range −6.602–12.699). The difference between young and old subjects was not significant ($p=0.256$, $t=-1.158$, $df=30$).

Behavioral results: task performance in young and old subjects During encoding, both age groups showed high accuracy in object judgments. There were no significant between-group differences in RTs and accuracy (RTs young: 963.8±49.7 ms; RTs older: 894.4±27.6 ms; accuracy young: 96.8±3.1%; accuracy older: 95.3±5.0%; all p-values >0.30). In the retrieval session, the accuracy of judging stimuli as old was comparable in young and old subjects (young, 84.6±2.3%; old, 80.0±2.6%; t=1.323, $df=30$, $p=0.196$). This indicates that the two groups did not differ with respect to remembering the items presented during encoding. A significant difference, however, was found with regard to accuracy in source memory judgments (young: 57.5±3.5%; old: 38.0±2.7%; $t=3.915$, $df=30$, $p<0.001$). A two-way repeated measures ANOVA on RTs with the within-subject factor spatial context judgment (correct, incorrect) and the between-subject factor age (young, older) revealed a significant main effect of spatial context judgment (CorSCR: 1,512.3±59.3 ms, FalSCR: 1,708.3±60.6 ms, $F(1,30)=35.634$, $p<0.001$) and an interaction between age and spatial context judgment ($p<0.005$, $F(1,30)=10.767$), but no main effect of age (young: 1,554.8±55.4 ms, older: 1,665.8±102.5 ms, $p=0.355$, $F(1,30)=0.883$).

The further presentation and discussion of results is restricted to the modulation of task-specific neural activations related to the individual stress level as represented by the cortisol response in young and old volunteers. Age-related differences in neural networks subserving contextual memory have been reported and discussed in detail elsewhere (Kukolja et al. 2008).

To investigate potential effects of prescan cortisol levels, we additionally calculated an equivalent multiple regression analysis using prescan cortisol values instead of the cortisol response to investigate the effect of putative glucocorticoid or mineralocorticoid occupation on the behavioral data. There was no association of prescan cortisol values on any tested variable and no interaction effect of age and prescan cortisol values (see supplementary material).

Association of the cortisol response with task performance in young and old subjects The multiple regression analysis revealed that, in young subjects, the cortisol response was positively correlated with the accuracy of spatial context judgments (expressed as the number of CorSCR, see Table 1 and Fig. 1a). This was not the case in older subjects, but there was no significant interaction effect between the cortisol response and age group. A significant interaction effect between age group and cortisol response, however, was observed in item recognition (expressed as the sum of CorSCR and FalSCR items; Table 1, Fig. 1b). This was due to a positive correlation of the cortisol response with item recognition in young subjects but no such effect in older subjects (Table 1, Fig. 1b). Thus, young subjects recognized more items correctly as previously seen when the cortisol response was higher, while this was not the case in older subjects.

There were further interaction effects between age group and cortisol responses with regard to RTs. These effects were observed for correct source memory judgments (CorSCR) and

Table 1 Multiple regression analysis of the effects of age group, cortisol response and their interaction on behavioral data such as the number of CorSCR items, FalSCR items, and RTs in young and older subjects during the retrieval session

Multiple regression analyses of behavioral data from retrieval						
Parameter	*Df*	R^2	Variable	Std. Beta	*t*	*p*
CorSCR items	(3, 28)	0.427	CR (young)	0.679	3.531	**<0.005**
			CR (old)	0.078	0.263	0.795
			Group	−0.474	−3.478	**<0.005**
			Group*CR	−0.269	−1.785	0.086
CorSCR + FalSCR items	(3, 28)	0.208	CR (young)	0.672	2.786	**<0.05**
			CR (old)	−0.240	−0.644	0.526
			Group	−0.097	−0.569	0.574
			Group*CR	−0.408	−2.158	**<0.05**
RTs (CorSCR)	(3, 28)	0.368	CR (young)	−0.221	−0.913	0.370
			CR (old)	1.044	2.791	**<0.01**
			Group	0.214	1.244	0.225
			Group*CR	0.566	2.982	**<0.01**
RTs (CorSCR + FalSCR)	(3, 28)	0.334	CR (young)	−0.251	−1.011	0.322
			CR (old)	1.078	2.815	**<0.01**
			Group	0.086	0.498	0.623
			Group*CR	0.595	3.059	< **0.01**

CR Cortisol response

for item recognition (CorSCR + FalSCR; Table 1, Fig. 1a). The interactions were due to a positive association of the cortisol response with RTs for CorSCR only and CorSCR + FalSCR in older subjects but no association with RTs for CorSCR and a nonsignificant trend for a negative association with RTs for CorSCR + FalSCR and in young subjects during retrieval (Table 1, Fig. 1b). Thus, older subjects reacted more slowly when the cortisol response was higher, while young subjects had a tendency for faster RTs.

Importantly, these data reflected a differential effect of the individual cortisol response in the two groups, while the mean cortisol response itself did not differ between groups.

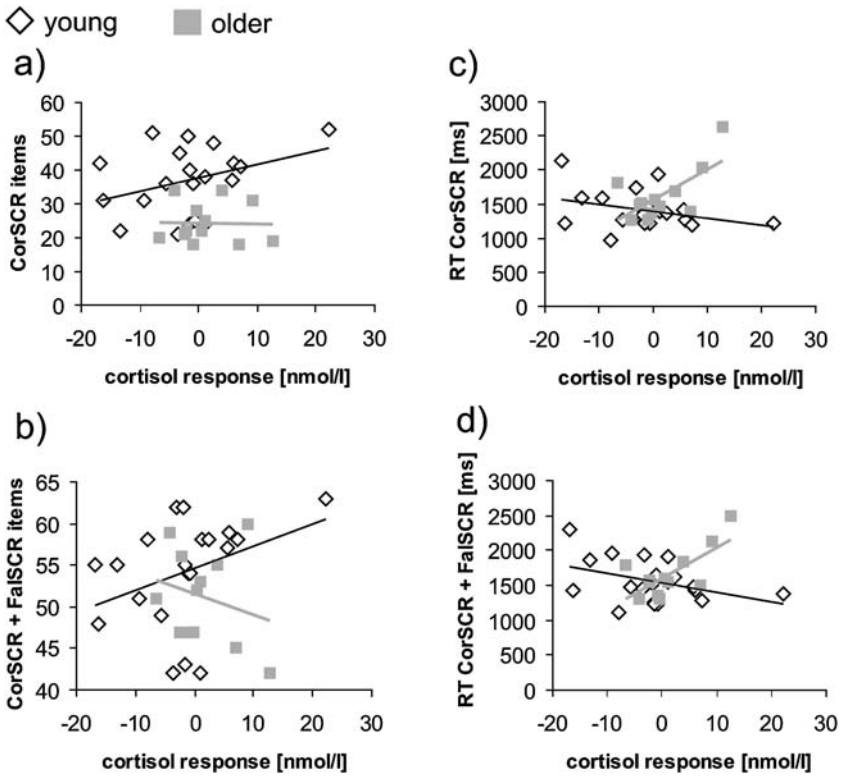

Fig. 1 Correlation between the cortisol response and **a** the number of CorSCR items, **b** the number of all items correctly recognized as "old" (CorSCR + FalSCR), **c** RT Medians for CorSCR trials, and **d** RT Medians for CorSCR + FalSCR trials together in young and older subjects

Analogous analyses of prescan cortisol values did neither reveal any associations with spatial context and item accuracy nor with RTs (all *p*-values were>0.05).

Neuropsychological tests There were no significant correlations between the cortisol response and any of the neuropsychological test scores acquired on a separate occasion (MWTB IQ estimate, CERAD immediate recall, CERAD free recall, CERAD recognitions, CERAD correct rejections, CERAD MMSE, word fluency, HAWIE digit span, MAC-Q; all *p*-values were>0.05).

fMRI data: encoding In several brain areas, neural activity during encoding of items that were later associated with correct source memory judgments (CorSCE) was positively related to the cortisol response in young subjects. These brain regions included the right middle frontal gyrus, the right superior parietal cortex, and the left temporo-occipital junction (Table 2a). There was no correlation of cortisol and encoding-related activity in older subjects. However, there was an interaction effect between cortisol response and age group on CorSCE-associated brain activity in the left middle frontal gyrus.

fMRI data: retrieval In several brain regions in older subjects, neural activity during correct retrieval of spatial contextual information (i.e., CorSCR trials) was negatively related to the cortisol response (i.e., neural activity decreased with an increasing cortisol response). Areas included the left middle frontal gyrus, the right inferior frontal gyrus, and the right hippocampal formation. The interaction effect between the cortisol response and age group in these areas was significant indicating that older subjects showed decreasing activity related to CorSCR trials with an increasing cortisol response while young subjects had a tendency for increasing activity (Table 2b, Fig. 2). A negative association of the cortisol re-

Table 2 Multiple regression analysis of the effects of age, cortisol response and their interaction on task-related activity identified by (a) the contrasts CorSCE > baseline during encoding and (b) CorSCR > baseline during retrieval

	Side	*x*	*y*	*z*	*Z* score	*vx*	Slope
a) Multiple regression analysis of neural activity data obtained during encoding							
Effect of the cortisol response on CorSCE > BL in young subjects							
Middle frontal gyrus	R	30	27	57	3.75	25	**(+)**
Precentral gyrus	R	−36	−6	66	4.22	32	**(+)**
Superior parietal cortex	R	21	−63	69	3.55	10	**(+)**
Superior parietal cortex	R	39	−45	60	4.33	11	**(+)**
Temporo-occipital junction	L	−51	−66	15	4.27	27	**(+)**
Superior occipital gyrus	L	−33	−84	33	3.87	14	**(+)**
Effect of the cortisol response on CorSCE > BL in older subjects							
No suprathreshold activations		0					
Age group × cortisol response interaction effect on CorSCE > BL							
Middle frontal gyrus	R	0	18	57	4.42	21	**y(+)o(-)**
b) Multiple regression analysis of neural activity data obtained during retrieval							
Effect of the cortisol response on CorSCR > BL in young subjects							
Middle frontal gyrus	L	−33	48	-6	3.67	16	**(-)**
Effect of the cortisol response on CorSCR > BL in older subjects							
Middle frontal gyrus	L	−39	39	24	4.35	10	**(-)**
Inferior frontal gyrus, pars opercularis	R	48	15	6	4.66	54	**(-)**
Postcentral gyrus	R	45	−24	27	3.92	19	**(-)**
Hippocampal formation	R	36	−18	−12	3.84	45	**(-)**
Temporo-occipital junction	L	−63	−48	18	3.92	13	**(-)**
Thalamus	R	6	−21	6	4.18	12	**(-)**
Cerebellum	R	21	−36	−33	4.05	14	**(-)**
Age group × cortisol response interaction effect on CorSCR > BL							
Middle frontal gyrus	L	−39	39	24	4.69	13	**y(+)o(-)**
Inferior frontal gyrus, pars opercularis	R	48	18	9	4.47	34	**y(+)o(-)**
Hippocampal formation	R	39	−18	−12	4.00	31	**y(+)o(-)**
Putamen	L	−24	0	15	3.63	11	**y(+)o(-)**
Temporo-occipital junction	R	45	−63	12	4.12	21	**y(+)o(-)**
Postcentral gyrus	R	45	−24	27	3.80	14	**y(+)o(-)**
Cerebellum	R	33	−45	−45	3.65	13	**y(+)o(-)**

Side: left (L) or right (R) hemisphere. (+) indicates a positive effect, (−) indicates a negative effect. *Y* young, *O* older, *VX* voxels.

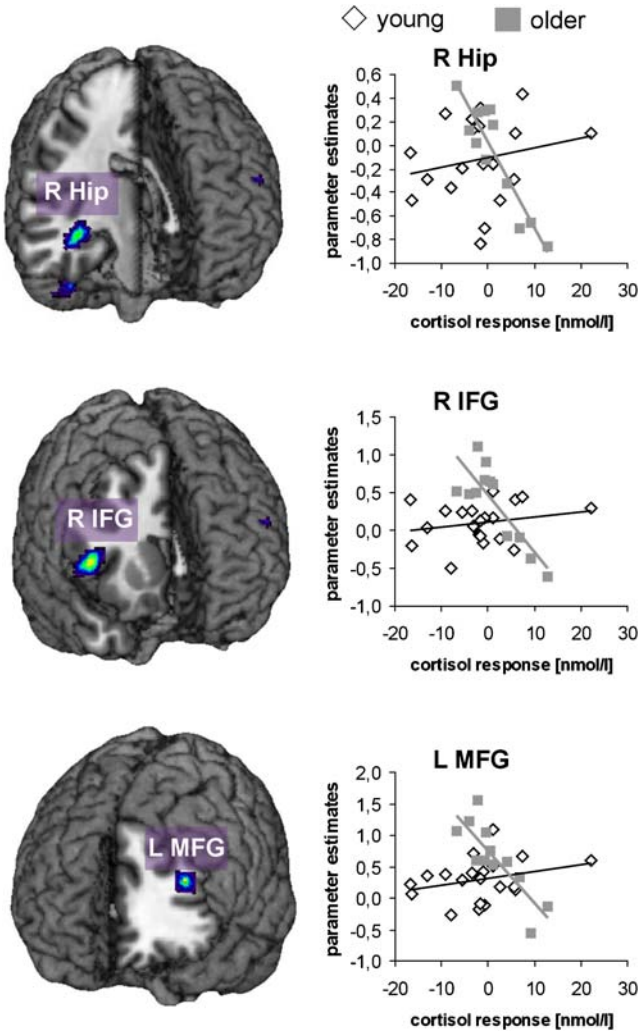

Fig. 2 Interaction effect of age group and cortisol response on brain activity revealed by the contrast CorSCR > baseline at retrieval. Activations are projected upon a 3D template brain provided by the visualization software MRIcroN (www.mricro.com). The graphs depict parameter estimates revealed by the contrast CorSCR > baseline (*y*-axis) plotted upon the cortisol response (*x*-axis) for both young and older subjects. Hip hippocampal formation, *IFG* inferior frontal gyrus, *MFG* middle frontal gyrus, *L* left, *R* right

sponse with activity related to CorSCR trials in young subjects was found only in the frontopolar part of the left middle frontal gyrus (Table 2b).

Discussion

In the present analysis, we observed a differential association of the individual cortisol response (ranging from negative to positive values) induced by the fMRI paradigm with spatial contextual memory performance in older as opposed to young subjects. The neural substrate of this finding was a differential responsiveness of task-related activity in several brain regions including the right hippocampus as well as the left and right prefrontal cortex to the cortisol response.

Cortisol response The cortisol response in our study can be regarded as a marker of the individual stress level experienced by the subjects while performing a cognitively challenging source memory task (Dickerson and Kemeny 2004), although some of the cortisol response values may have been influenced by diurnal variations in cortisol secretion. Rather than comparing a stress with a no-stress condition, we report the associations of behavioral and neural measures with a continuum of cortisol response values.

Nevertheless, the task was cognitively challenging for the participants particularly during the retrieval session, as evidenced by high error rates. The MRI environment may have been an additional stressor for some subjects independent of the task to be performed as similar increases in cortisol responses have been observed during other fMRI experiments (Tessner et al. 2006). Importantly, young and older subjects neither differed significantly in their cortisol level before or after the fMRI session nor in their cortisol response. Thus, the observed between-group differences of the association of the cortisol response with behavioral and neural measures were not biased by differences in the cortisol response itself (Lupien et al. 2007). Furthermore, the results were not confounded by pre-scan salivary cortisol levels since these values were included into the multiple regression analyses as a nuisance variable. The pre-scan salivary cortisol levels themselves did not show any correlation with behavioral data. The mean cortisol differences were relatively little compared to those observed in studies specifically aimed at exposing subjects to psychological stress (Wolf et al. 2001b). However, some subjects did show cortisol responses similar to those after psychosocial stress exposure (Wolf et al. 2001b), which validates the use of regression analyses to investigate the association of the individual cortisol response with behavioral measures and neural activations.

Behavioral data Young subjects showed a positive association of cortisol responses with item memory and with the memory for the respective spatial context. This was not the case in older subjects. In older subjects, the association of the cortisol response with item memory was even inverse, leading to increased reaction times with higher cortisol responses. The reaction times likely reflected the time a subject needed to match the presented stimulus with the pool of objects stored in memory and if necessary to retrieve the respective spatial contextual information. They are therefore an additional measure for retrieval efficiency.

From the behavioral data alone, it is difficult to assess whether the increasing cortisol responses in young subjects are mainly associated with an increased efficiency at encoding

or retrieval. However, the assumption that predominantly encoding was influenced in young subjects in the present study is supported by the neural data, showing a positive association between the cortisol response and task-related brain activity during encoding in this group (see discussion below). While this is in line with previous findings that acute cortisol elevations can enhance episodic memory encoding (Abercrombie et al. 2003; Buchanan and Lovallo 2001; Diamond et al. 2007; Het et al. 2005; Joels et al. 2006), it is possible that the effects observed during encoding in our study were not mediated by cortisol (which was probably not yet elevated shortly after the onset of the experiment) but were rather initiated by other neuromodulators such as noradrenaline or corticortopin-releasing hormone (CRH, see also discussion of fMRI data during encoding).

The results in older subjects on the other hand are in accordance with previous studies showing a negative effect of cortisol on episodic memory retrieval (de Quervain et al. 2003; Het et al. 2005; Wolf et al. 2004). Again, the fMRI data in the present study support the hypothesis that the cortisol response affected retrieval rather than encoding in older subjects since cortisol response induced modulations of neural activity were primarily found in the retrieval session (see discussion below).

Theoretically, one could argue that the causality was inverse, i.e., that worse performance as reflected in higher RTs induced higher cortisol responses within the group of older subjects. The fact that young subjects showed a better performance with increasing cortisol responses rather speaks against this hypothesis because in this case better performance would have led to increasing stress, which does not seem plausible. A further argument against an inverse causality is the lack of any association of the cortisol response with neuropsychological test scores which were obtained on a separate occasion. If generally bad memory performance was the reason for greater stress in the memory task in some subjects (reflected in higher cortisol responses), then one would also expect a negative correlation between other memory scores and the cortisol response, which was not the case.

Although there were no general age-related differences in cortisol measures in the current study, the differential association of the cortisol responses and RTs highlights an important issue in behavioral and fMRI studies dealing with age effects on cognition, i.e., behavioral and fMRI differences between age-groups may be biased by differential stress levels between young and older subjects (Lupien et al. 2007).

fMRI data: encoding In young subjects, the cortisol responses were associated with increased activity in several brain areas such as the right middle frontal gyrus, right superior parietal cortex, the right precentral gyrus, and the left temporo-occipital junction. Such a pattern was not found in older subjects. In the right middle frontal gyrus, an area which has frequently been found to be involved in episodic memory encoding (see Rajah and D'Esposito 2005 for review) the activation pattern was even inverse in older subjects leading to a significant interaction effect between the cortisol response and age group. Increased activity in these areas associated with increasing cortisol responses during the first session could have been the substrate for more effective encoding in young subjects, leading to better task performance during retrieval. This would be in line with reported beneficial effects of stress during the learning episode on subsequent memory consolidation (Abercrombie et al. 2003; Buchanan and Lovallo 2001; Diamond et al. 2007; Het et al. 2005; Joels et al. 2006). Stress-induced increases of lateral prefrontal cortical metabolism and perfusion have been observed in earlier studies (Kern et al. 2008; Wang et al. 2005). Such increases have been associated with increased vigilance and attention following stressful situations.

Assuming that the cortisol response reflected the individual stress level, it is conceivable that the observed effects particularly during the early phase of encoding were not directly mediated by cortisol but rather by, e.g., a concomitant noradrenalin or CRH response for several reasons. First, glucocorticoid receptor action is time consuming because it acts via time-consuming gene transcription. Second, even if one assumes that glucocorticoids may also act rapidly via non-genomic mechanisms (Joels et al. 2006; Joels and Krugers 2007), cortisol was probably not sufficiently elevated at encoding shortly after the onset of the experiment. Third, pre-scan cortisol values (which should correspond to the initial occupation of mineralocorticoid and glucocorticoid receptors) were not correlated with any behavioral measure (see supplementary material), indicating that the effects observed went beyond mere glucocorticoid action.

There is sufficient evidence that an elevation of the concentration of noradrenalin modulates memory performance and neural activations, particularly in the amygdala which are thought to play a central role in stress and emotional processing (Chamberlain et al. 2006; Hurlemann et al. 2005; van Stegeren et al. 2005).

fMRI data: retrieval Another central finding, possibly providing an explanation for the behavioral data, was the interaction effect between the cortisol response and age group on neural activations during retrieval. In older subjects, several cortical regions showed an association of the cortisol response with neural activity linked to correct retrieval of contextual spatial information. In all these regions (including the left middle frontal gyrus, the pars opercularis of the right inferior frontal gyrus, the right hippocampal formation, and the left temporo-occipital junction), this effect was negative, meaning that a higher cortisol response was associated with less neural activity during trials with a correct spatial context judgment. Since these regions, in particular the left middle

and right inferior frontal gyri as well as the right hippocampal formation, are typically involved in episodic memory retrieval (Burgess et al. 2001, 2002; Cansino et al. 2002; Eldridge et al. 2000; Iidaka et al. 2006; Kukolja et al. 2008; Lundstrom et al. 2005), the decrease in activity could be regarded as the substrate for a decreased efficiency in retrieving items and their respective spatial contextual information which resulted in longer RTs as observed in older subjects.

The hippocampal formation has been found reactive to stress in earlier investigations: studies with rodents have observed normal to increased activity patterns of hippocampal cells at moderate glucocorticoid concentrations but reduced post-stress activity at higher glucocorticoid concentrations (see de Kloet et al. 1999, for review). In rats, acute and chronic exposure to stress leads to alterations in the neuronal circuitry between the hippocampal formation and the prefrontal cortex resulting in working memory and learning impairments (Cerqueira et al. 2007; Roozendaal et al. 2006a). In humans, cortisol has frequently shown a negative effect on declarative memory retrieval which was associated with a reduction in hippocampal activity (de Leon et al. 1997; de Quervain et al. 2003; Oei et al. 2006, 2007). Stress-induced deactivations in the limbic system including the hippocampal formation have been observed even independently from memory paradigms (Pruessner et al. 2008). Conversely, other investigators have suggested a reciprocal association between cortical activity and cortisol secretion. Regions mediating cognitive control and voluntary modulation of emotions such as the medial prefrontal cortex seem to attenuate cortisol excretion either by direct interference with the HPA axis by reduction of hypothalamic activity (Ahs et al. 2006) or indirectly by controlling activity of emotionally relevant areas such as the amygdala (Urry et al. 2006). Possibly, in older subjects, such regulatory mechanisms are less pronounced than in younger subjects.

The observed behavioral and neural activity associations with acute changes in the cortisol concentration could be the basis for the deleterious effect of chronic elevations of cortisol on memory performance and neural integrity in older subjects. Prolonged elevations of basal plasma cortisol concentrations have been observed to be associated with reduced hippocampal volume and deficient memory performance in otherwise healthy elderly subjects (Lupien et al. 1998, 2005; Wolf et al. 2005) but also in patients with states of pathologically elevated glucocorticoid concentrations as found, e.g., in Cushing's disease (Forget et al. 2000; Sapolsky 2000; Starkman et al. 1992, 1999).

Glucocorticoid action in the brain Whether cortisol exerts an excitatory or inhibitory influence on neurons depends on the ratio at which cortisol occupies intracellular high-affinity mineralocorticoid and low-affinity glucocorticoid receptors (de Kloet et al. 1999): predominant mineralocorticoid receptor occupation at low cortisol concentrations is linked to stable neuronal responses to stimulation but a shift to a higher glucocorticoid receptor occupation at elevated cortisol concentrations reduces cellular activity (de Kloet et al. 1999; Reichardt and Schutz 1998). While this is true for hippocampal neurons, other brain areas such as the basolateral amygdala can show an enhancement of neuronal excitability in response to glucocorticoid administration (Duvarci and Pare 2007).

Although some studies suggest that the amygdala mediates corticoid effects on cognition (Roozendaal et al. 2006a), this region did not show any correlation between its activity and the cortisol response. The effect of cortisol on cognition is thought to depend upon noradrenergic activation of the amygdala, which can be observed in states of emotional arousal (Canli et al. 2000; de Quervain et al. 2007; Hurlemann et al. 2005; McIntyre et al. 2003; Nathan et al. 2004; Roozendaal et al. 2006a, b; Zald 2003). The lack of a correlation of the cortisol response with amygdaloid activation can probably be reduced to the fact that in the present study no emotional stimulus material was used.

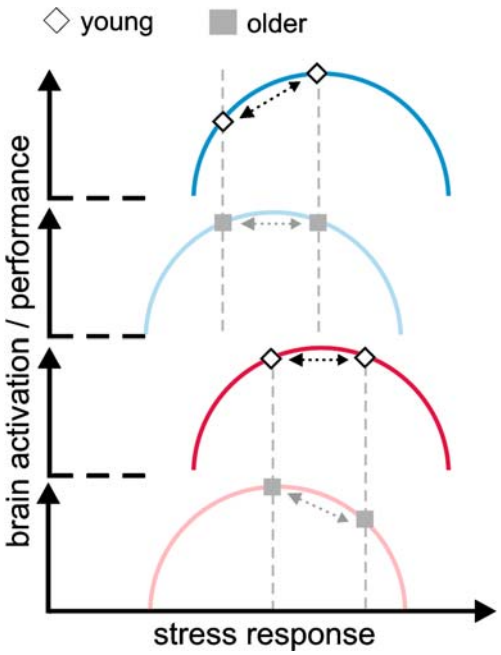

Fig. 3 Schematic illustration of theoretical u-shaped relationship between stress level (on the *x*-axis) and brain activity/task performance (on the *y*-axis) according to the Yerkes–Dodson law (see text). Putative performance curves for encoding are depicted in *blue*, those for retrieval in *red*. In this model, the performance curves of older subjects (*light blue* for encoding, *light red* for retrieval) are shifted to the left relative to the curves of young subjects due to a higher demand of the same task on older subjects. The left and right data points for each group (*empty diamonds* for young, *grey boxes* for older subjects) are positioned at the lowest (*left*) and highest (*right*) arousal states within each group. Note that the curves do not depict absolute values but rather trends within each age group separately

Theoretical considerations One possible explanation for the behavioral and fMRI findings could be that young and older subjects have differentially positioned u-shaped curves of the relationship between arousal (reflected in the cortisol response) and task performance/brain activity. The Yerkes–Dodson law states that task performance first improves and then deteriorates with increasing arousal (see Diamond et al. 2007 for review; Yerkes and Dodson 1908). This relationship is dependent on task difficulty. However, higher task difficulty shifts the u-shaped curve more to the left, indicating that optimal performance is reached at lower arousal levels (Diamond et al. 2007). In the extreme case of very simple tasks, increasing arousal can be associated with a linear increase of performance. We suggest that an analogous relationship exists between arousal and brain activity underlying behavioral performance.

Since the group of older subjects performed worse in the spatial contextual memory task in the present study, it is obvious that the task was more difficult for older than for young subjects. It is conceivable that this resulted in a leftward shift of the u-shaped curve of older subjects in relation to the curve of younger subjects (Fig. 3). This would explain why during the relatively easy encoding session, a higher cortisol response was associated with higher activations in young subjects (as a substrate for more efficient encoding which resulted in better item recognition during subsequent retrieval) but with no change in older subjects. During the more demanding retrieval session, stress levels were higher (or the u-shaped curves were further shifted to the left because of higher task difficulty) resulting in no correlation (or still a positive correlation) of the cortisol response with retrieval in young subjects but a negative tendency in older subjects (Fig. 3).

Of course, this model is a simplification and does not account for, e.g., the possibility of a differential interaction of the cortisol response on the aging brain, but it might provide a plausible explanation for some of the observations.

Limitations of the present study One limitation of the study may arise from the fact that genders were mixed in the two age groups. It is known that young and older (i.e., postmenopausal) women have a different hormonal status which may result in a differential neuroendocrine response. Although gender effects are statistically controlled for in the present analysis, further studies with larger samples of young and older men and women are needed to investigate possible gender effects.

In spite of the fact that there is sufficient evidence that stress induces cortisol increases, additional subjective measures of stress experience would have been advantageous to establish a closer association between the actually perceived individual stress and the individual cortisol responses. Furthermore, although the time of day was included as a nuisance covariate into the multiple regression model thereby minimizing diurnal effects on the results reported, it would increase the validity of the data in future studies to standardize the time of day. Finally, although many participants in the present study showed cortisol responses indicating a stress reaction, the task used in the present study was not explicitly designed to induce stress responses. Hence, future studies using specific stress tasks are needed to further explore this issue.

Conclusion This study contributes to understanding the effects of aging on neuroendocrine influences on cognition. The present data provide evidence for age-related differences in the susceptibility of memory-specific brain regions such as the hippocampal formation, the middle and inferior frontal gyri to changes in endogenous cortisol release. Although in our study the two age groups did not differ in their cortisol measures, the present results highlight that the individual stress level should be taken into account when age-effects on cognition are studied.

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