Behavioral/Systems/Cognitive

Stressed Memories: How Acute Stress Affects Memory Formation in Humans

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Stressful, aversive events are extremely well remembered. Such a declarative memory enhancement is evidently beneficial for survival, but the same mechanism may become maladaptive and culminate in mental diseases such as posttraumatic stress disorder (PTSD). Stress hormones are known to enhance postlearning consolidation of aversive memories but are also thought to have immediate effects on attentional, sensory, and mnemonic processes at memory formation. Despite their significance for our understanding of the etiology of stress-related mental disorders, effects of acute stress at memory formation, and their brain correlates at the system scale, remain elusive. Using an integrated experimental approach, we probed the neural correlates of memory formation while participants underwent a controlled stress induction procedure in a crossover design. Physiological (cortisol level, heart rate, and pupil dilation) and subjective measures confirmed acute stress. Remarkably, reduced hippocampal activation during encoding predicted stress-enhanced memory performance, both within and between participants. Stress, moreover, amplified early visual and inferior temporal responses, suggesting that hypervigilant processing goes along with enhanced inferior temporal information reduction to relay a higher proportion of task-relevant information to the hippocampus. Thus, acute stress affects neural correlates of memory formation in an unexpected manner, the understanding of which may elucidate mechanisms underlying psychological trauma etiology.

Introduction

Information encoded into memory during stressful experiences is generally well remembered (Kim and Diamond, 2002), especially if this information is relevant to the stressor (Joëls et al., 2006; Sandi and Pinelo-Nava, 2007; Smeets et al., 2009). Although this phenomenon represents adaptive behavior, dysregulation of the underlying mechanism might result in psychological trauma and thus potentially mental disease (McEwen, 2004; de Kloet et al., 2005). Past research has put strong emphasis on the mechanisms by which acute stress enhances memory consolidation (Roozendaal et al., 2006). It is widely assumed that rapidly unfolding neurochemical events during the initial stress phase exert immediate effects on attentional, sensory, and mnemonic processes (de Kloet et al., 2005). However, such putative effects of acute stress have received little attention and remain poorly understood.

The effects of stress on memory are thought to be mediated through hormones and neurotransmitters released by two interacting effector systems: the (nor)epinephrine (NE) sympathetic system and the hypothalamic–pituitary–adrenal (HPA) axis. Under stress, the sympathetic system, with the locus ceruleus (LC) at its core, shifts toward a tonically active state (Aston-Jones and Cohen, 2005; Valentino and Van Bockstaele, 2008). This shift causes an increase in NE tone almost in the entire brain, including the medial temporal lobe (MTL) (Valentino and Van Bockstaele, 2008; Sara, 2009), the key structure of the declarative memory system (Squire and Zola-Morgan, 1991). This increased NE tone, which is associated with peripheral effects such as pupil dilation, supports neural plasticity that underlies memory formation (Roozendaal et al., 2006) and causes a surge of arousal that is thought to lead to hypervigilance and prioritized processing of information relevant to the stressor (Aston-Jones and Bloom, 1981; Ramos and Arnsten, 2007). On a slightly longer timescale, the HPA axis increases the release of glucocorticoids, which also modulate MTL plasticity (Lupien and Lepage, 2001; de Kloet et al., 2005; Roozendaal et al., 2006; McEwen, 2007). Together, neuromodulators active during acute stress can therefore be hypothesized to induce a system level reorganization of mnemonic processes, geared toward more effective memory encoding.

To tackle this issue, we used functional magnetic resonance imaging (fMRI) to probe effects of controlled stress induction on the neural substrates of memory formation. To satisfy the putative requirements for stress-enhanced memory to occur (Joëls et al., 2006; Sandi and Pinelo-Nava, 2007), we maximized overlap between stressor and learning material by fully embedding a learning task in a stressful context created by strongly aversive movie clips (Qin et al., 2009; van Marle et al., 2009). To isolate

neural activity related to successful memory encoding, we used a well established subsequent memory paradigm (cf. Dolcos et al., 2004). Crucially and in contrast to previous studies that looked into the effects of arousing items on memory formation (Cahill, 2003; Richardson et al., 2003; Dolcos et al., 2004), we implemented a crossover design with separated stress and nonstress control sessions. Thus, the present study allowed us to assess prolonged modulations of mnemonic operations caused by a protracted state of acute stress.

Materials and Methods

Participants

Eighteen young (ages, 19–31 years; median, 22 years), right-handed, healthy male volunteers gave informed consent to participate in the study. Individuals who met any of the following criteria were excluded from participation: history of head injury, treatment with psychotropic medications, narcotics, β-blockers, steroids, or any other medication that affects CNS or endocrine systems, medical illness within the 3 weeks before testing, self-reported mental or substance use disorder, daily tobacco use, regular nightshift work, current stressful episode or major life event, previous exposure to slides used in the study [i.e., International Affective Picture System (IAPS) (Lang et al., 1999)], and regularly viewing extremely violent movies or playing violent computer games. Moreover, volunteers with high scores on depression [score above 8 on the Beck Depression Inventory (Beck et al., 2002)] were excluded from participation. The study was in accordance with institutional guidelines of the local ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen, The Netherlands) and the declaration of Helsinki.

Study design

In a counterbalanced crossover design, all men underwent two sessions, separated by 1 month, of intentional episodic memory encoding during fMRI. Memory was tested 24 h after each fMRI session by cued recall (CR). Both neutral and negative pictures were encoded, which were either embedded in a stressful or neutral control context created by short movie clips (Fig. 1). This allowed us to investigate brain activation during memory formation in a coherent stressful experience as a function of later remembrance, both within [contrasting brain activation during the processing of subsequently remembered and forgotten items (Wagner et al., 1999)] and between (relating brain activation to memory performance across subjects) subjects. Physiological [cortisol level, heart rate (HR), and pupil dilation], and psychological [negative affect (NA)] indices were measured to confirm successful stress induction. Data were analyzed with the factors stress (stress induction vs control context), subsequent memory (later remembered vs later forgotten items), and item valence (negative vs neutral pictures).

Procedure

Before arrival. To minimize differences in baseline cortisol levels, we instructed participants not to use any recreational drugs for 3 d and to refrain from drinking alcohol, exercising, and smoking for 24 h before each session. Furthermore, participants were requested not to brush their teeth, floss, or eat and drink anything but water for 2 h before all sessions, enabling adequate saliva sampling for cortisol assessment. To reduce the impact of diurnal variation in cortisol levels, all testing was performed in the afternoon, between 2:00 P.M. and 6:00 P.M., when hormone levels are relatively stable.

Arrival. On the first day, participants rested 30 min before taking the first saliva sample. To increase familiarity with the procedure and minimize task repetition effects, participants were explicitly informed about
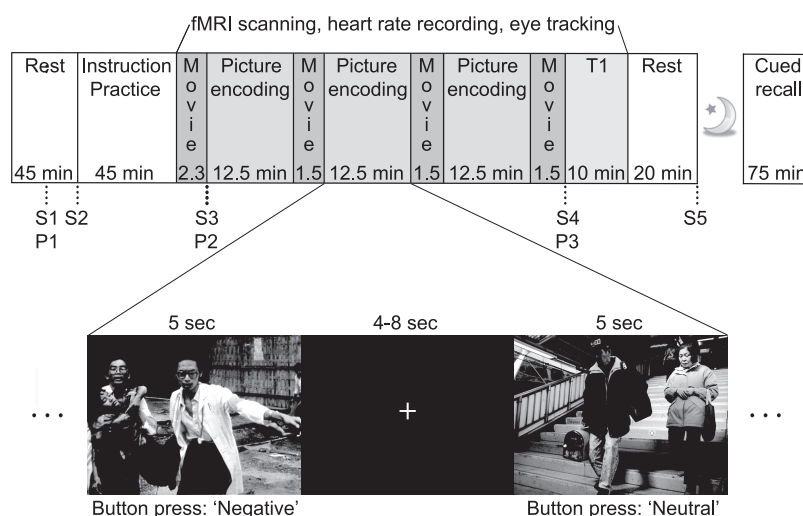
Figure 1. Experimental design. IAPS pictures (Lang et al., 1999) were encoded during fMRI scanning in either a stressful or a neutral control condition generated by short movie clips. Psychological and physiological measures were obtained to monitor the effectiveness of stress induction. Memory was tested 24 h later in a cued recall test. S, Saliva sample; P, PANAS questionnaire (Watson et al., 1988).

all details of the memory experiment. A financial reward was promised proportional to the participant's performance in the recall test to encourage encoding. Furthermore, participants were asked to complete Spielberger's Trait Anxiety Inventory (van der Ploeg et al., 1980) and the NEO-Five Factor Inventory (Costa and McCrae, 1992).

Scanning. Participants lay supine in the scanner and viewed the screen through a mirror positioned on the head coil. They were asked to lie as still as possible, keep their eyes open, and look directly and continuously at the center of the screen in front of them. Four movie fragments were used to create the appropriate context, shown before, between, and at the end of picture encoding (dividing the encoding session in three blocks) (Fig. 1). Participants were instructed to view each movie clip and picture for the entire time that it was displayed. Pictures belonged to two categories, with either a neutral or negative picture valence. Participants were asked to memorize and rate the valence of each picture. Ratings were given with right-hand button presses, with the index finger for negative and the middle finger for neutral pictures. Pictures were shown in a pseudorandom order (no more than two pictures of the same valence consecutively), and all first slides were neutral to avoid ceiling effects in recall that might result from the combined effect of arousal and primacy on memory. Slides were presented for 5 s with a 4–8 s intertrial interval (fixation cross). After completion of the encoding task, a structural scan was performed.

Subsequent memory test. Participants came back the subsequent day to perform a cued recall test, lasting 75 min. One- or two-word written cues for each picture (with similar valence as the picture) were provided, describing the readily identifiable gist of the picture, i.e., which is the most salient feature of the scene depicted on the picture. Participants were asked to write down as many characteristics of all pictures as they possibly could remember, providing enough relevant characteristics so that an outsider could identify each picture and discriminate it from similar studied pictures (Dolcos et al., 2004). A short introduction was written to help the participants in listing characteristics. One rater evaluated initially the written descriptions provided by the participants, and only pictures with a description that allowed both identification and discrimination were classified as remembered. Pictures with no recollection of characteristics were considered forgotten. Picture descriptions that could not clearly be linked to a particular picture were scored as a nonresponse and not included in the analyses. Subsequently, a second rater, blind to the study condition, independently re-rated all responses in the memory test to probe reliability. Inter-rater correspondence was very high (95.6%) and comparable

with other studies using similar designs (Buchanan and Lovallo, 2001; Payne et al., 2006, 2007).

Stimulus materials

Stressor. Four short movie fragments were used to create the proper context (1×140 s, 3×90 s). They were either selected from a distressing movie [Irréversible (2002), Gaspar Noé] or a neutral control movie [Comment j'ai tué mon père (2001), Anne Fontaine]. Selected fragments were comparable in amount of speech, human presence, luminance, and language. The stressful movie clips contained scenes with aggressive behavior and violence against men and women. Occasionally, people in the video could be heard shouting and crying out in anger, pain, or distress. Previous studies have confirmed the effectiveness of these movie clips in inducing stress (Qin et al., 2009; van Marle et al., 2009). Although considerably distressing, the film content was approved by the NICAM (Dutch Institute for Audiovisual Media) for viewers above 16 years. Participants were informed before the experiment that watching the film could be stressful and that they could terminate the experiment at any point. This stress induction method was chosen because it meets the criteria described by Joëls et al. (2006) for stress-enhanced memory to occur, i.e., close spatiotemporal proximity and content overlap of stressor and task (the memory encoding was part of a continuous and coherent stressful episode experienced within an fMRI environment). This overlap in content was achieved by parallelizing studied pictures and movies based on content features, both depicting real-life, emotionally salient stimuli. To be more precise, the movies used in the stress condition contained, for example, male to male and male to female violence, mutilations, and injuries, which were also present in many negative IAPS photographs. There was also considerable overlap between the neutral movie and neutral pictures. Examples of scenes shown in both are, for example, people eating, talking, and walking.

Pictures. Three stimulus sets were created for picture encoding, two of which were used per participant. Each set consisted of 80 negative and 80 neutral pictures, supplemented with 41 null events (fixation). Pictures were selected from both a standard set of affective pictures [IAPS (Lang et al., 1999)] and an additional set of newly rated pictures. New pictures were downloaded from the internet and selected on the authors' assessment of emotionality and similarity to IAPS pictures. New pictures were rated on a scale from 1 to 9 on both arousal and valence using the Self-Assessment Manikin (SAM) scales (Bradley and Lang, 1994) by an additional group of 20 male volunteers. To ensure reliable rating that did not significantly differ from IAPS ratings and to serve as a reference frame, positive and negative IAPS pictures were added to this test set. All selected negative slides were chosen for their moderate-to-high arousal quality (average $\pm$ SE arousal score, 5.5 ± 0.7) and negative valence (average $\pm$ SE valence score, 3.1 ± 0.7), rated on a 1–9 point rating scale as determined by the SAM (Bradley and Lang, 1994). Neutral slides were selected for their relatively low arousal (average $\pm$ SE arousal score, 2.5 ± 0.7) and neutral valence (average $\pm$ SE valence score, 5.3 ± 0.3). Used picture sets contained $\sim$50% newly rated neutral and 15% newly rated negative pictures and were matched on chromatic features and complexity, whereas overlap in content within one set was minimized. Used stimulus sets did not differ in mean arousal and valence ratings.

Stress measures

Saliva collection and analysis. Cortisol levels were measured from saliva at five time points: baseline measurements at the beginning of the experiment (twice) ($t = 30$ and 45 min), immediately after the first movie clip ($t = 90$ min), immediately after the last movie clip ($t = 135$ min), and at the end of the experiment ($t = 165$ min).

Saliva was collected using a commercially available collection device (Salivette; Sarstedt). For each sample, the participant first placed the cotton swab provided in each Salivette tube in his mouth and chewed gently on it for 1 min to produce saliva. Third and fourth samples were taken in the scanner. Swabs were handed over to the participants, and they were instructed not to move their head while chewing. The swab was then placed back in the Salivette tube, and the samples were stored in a freezer at $-25°C$ until assayed. Laboratory analyses were performed at the Department of Biopsychology, Technical University of Dresden

(Dresden, Germany). After thawing, Salivettes were centrifuged at 3000 rpm for 5 min, which resulted in a clear supernatant of low viscosity. Salivary free cortisol concentrations were subsequently measured using a commercially available chemiluminescence immunoassay with high sensitivity of 0.16 ng/ml (IBL Inc.). For analyses, area under the curve with respect to increase was calculated and analyzed for cortisol levels expressed as baseline percentage of each session (average level of measurements 1 and 2).

Heart rate. Cardiac rhythm of the participants was measured during scanning, using a pulse oximeter placed on their left index finger. Participants were instructed to keep their hands as still as possible during the measurement. Heart rate frequency was calculated using in-house software. Data of one subject was discarded from analyses because of excessive artifacts in the recorded signal.

Pupil diameter. A commercial MR-compatible eye-tracking device from SensoMotoric Instruments (MEyeTrack-LR) mounted on the scanner bed was used to measure eye movements and pupil diameter at a sampling rate of 50 Hz. Moreover, eye-tracking confirmed attentive viewing of all slides and movie fragments.

Eye pupil data were analyzed using in-house software implemented in Matlab 7.5 (MathWorks), which was based on methods described previously by others (Siegle et al., 2003). Eyeblink artifacts were identified by differentiating the signal to detect eye pupil changes occurring too rapidly to represent actual dilation. Blinks were removed from the signal using linear interpolation. Scanner pulses recorded simultaneously enabled synchronization with stimulus presentation. Pupil diameter for each trial was normalized to the average 1 s prestimulus onset baseline. The averaged normalized pupil diameter during picture presentation was used as response measure. These were collapsed over trials within stress induction and picture valence conditions. Because of data loss or excessive artifacts in the recorded signal in either of the sessions, data of five subjects were not included into analyses. It is important to note that this method does not measure absolute pupil diameter.

Psychological measures. Mood state was assessed using the Positive and Negative Affect Schedule (PANAS) questionnaire (Watson et al., 1988) at three time points: at the beginning of the experiment ($t = 30$ min), immediately after the first movie clip ($t = 90$ min), and immediately after the last movie clip ($t = 135$ min). Picture valence ratings (neutral or negative), which were obtained during picture encoding blocks, were scored as either corresponding ("correct") or not corresponding ("incorrect") with a priori categorizations. Furthermore, average reaction times (RTs) were calculated for those items with correct rating.

Behavioral and physiological statistical analysis. Behavioral and physiological data were analyzed in SPSS 15.0 (SPSS) using repeated measures ANOVAs and paired samples t test statistics. When no main effects or interactions involving the order factor were significant, this factor was omitted. Furthermore, in cortisol data analyses, the difference in time of day between both sessions was entered as a covariate. α was set at 0.05 throughout.

MRI acquisition. Participants were scanned in a Siemens TIM Trio 3.0 Tesla MRI scanner equipped with an eight-channel phased array head coil. Blood oxygenation level-dependent T2*-weighted gradient echo planar images (EPIs) were acquired with the following parameters: repetition time (TR), 2.18 s; echo time (TE), 25 ms; flip angle (FA), 90°; 37 axial slices approximately aligned with anterior commissure–posterior commissure plane; slice-matrix size, 64×64; slice thickness, 3.0 mm; slice gap, 0.3 mm; field of view (FOV), 212×212 mm^2. Because of its relatively short TE, this sequence yields optimal contrast-to-noise ratio in the medial temporal lobe.

A high-resolution anatomical image was acquired for each participant using a T1-weighted three-dimensional magnetization-prepared rapid gradient echo sequence combined with generalized autocalibrating partially parallel acquisitions (GRAPPA) (Griswold et al., 2002). The following parameters were used: TE, 2.96 ms; TR, 2300 ms; FA, 8°; FOV, $256 \times 256 \times 192$ mm; voxel size, 1 mm isotropic; GRAPPA acceleration factor 2. The total duration of each MRI session was $\sim$1 h.

fMRI data analysis. Data were analyzed using statistical parametric mapping software (SPM5; University College London, London, UK) and in-house software. The first five EPI volumes were discarded to allow for T1 equilibration. Before analysis, the images of the three encoding blocks

were separately motion corrected using rigid body transformations and least sum of squares minimization. Subsequently, they were temporally adjusted to account for differences in sampling times across different slices. All functional images were then coregistered with the high-resolution T1-weighted structural image using normalized mutual information maximization. The anatomical image was subsequently used to normalize all scans into MNI152 (Montreal Neurological Institute) space. All functional images were resampled with a voxel size of 2 mm isotropic. Finally, all images were smoothed with an isotropic 8 mm full-width at half-maximum Gaussian kernel to accommodate residual functional/anatomical variance between subjects.

Data were analyzed using a general linear model, in which individual events were modeled based on stress, subsequent memory, and item valence. Regressors were temporally convolved with the canonical hemodynamic response function of SPM5. The six covariates corresponding to the movement parameters obtained from the realignment procedure were also included in the model. To reduce unspecific differences between scan sessions, global normalization using proportional scaling was applied. The single-subject parameter estimates from each session and condition obtained from the first-level analysis were included in subsequent random effects analyses. For the second-level analysis, a factorial ANOVA was used, with stress induction (stress vs control context), picture valence (negative vs neutral), and subsequent memory (remembered vs forgotten) as within-subject factors. α for statistical tests was set at 0.05, family-wise error rate corrected using Gaussian random field theory. Based on our a priori hypothesis about their involvement in memory and attention, data for the regions of interest—MTL and ventral visual stream—were corrected for a reduced search region (based on their size) and small volume corrected using a sphere with 15 mm radius. Statistical tests for all other regions corrected for a whole-brain search region.

To test the regional overlap between the main effects of memory and stress, conjunction analyses were performed using the minimum statistic compared with the conjunction null method as implemented within SPM5 (Nichols et al., 2005). We used a reduced search volume with a radius of 10 mm (approximating the underlying spatial resolution of the fMRI signal) centered on the maxima of the main contrasts as proposed by Friston et al. (2005). For purpose of visualization of the overlap of both contrasts, the less conservative minimum statistic compared with the global null method with a threshold of $p < 0.001$, uncorrected, was used in Figure 3C.

To assess the relationship between neural activity and memory performance across subjects, mean activity of the anatomically defined hippocampus was extracted [using the automated anatomical labeling of activations (Tzourio-Mazoyer et al., 2002)], and the differences in responses between the stress and control conditions were entered in regression analyses as a predictor for the difference in memory performance. Visualizations of activations were created using MRIcron (http://www.sph.sc.edu/comd/rorden/mricron/) by superimposing statistical parametric maps thresholded at $p < 0.001$, uncorrected, onto a canonical T1-weighted image in standard MNI152 space.

Results

Effectiveness of stress induction: physiological measures
Physiological measures confirmed successful stress induction. Area under the curve measures of salivary cortisol levels indicated that HPA axis activity was elevated throughout the picture encoding procedure in the stress condition ($F_{(1,15)} = 6.49$; $p = 0.02$) (Fig. 2A). Moreover, heart rate frequency (mean $\pm$ SD; $HR_{control}$, 59.26 $\pm$ 9.36 beats per minute; HR_{stress}, 65.95 $\pm$ 9.69 beats per minute), which is associated with elevated sympathetic tonus, was increased ($F_{(1,16)} = 12.34$; $p = 0.003$). Finally, pupil dilation responses to pictures were decreased ($F_{(1,11)} = 4.90$; $p = 0.05$) (Fig. 2B). Given the direct association of LC activity and pupil dilation, this finding is consistent with the notion that phasic LC responses diminish against a background of enhanced tonic activity (Aston-Jones and Cohen, 2005). Moreover, in agreement
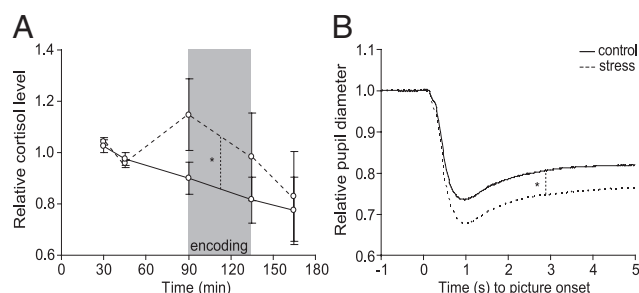
Figure 2. Physiological effects of stress. *A*, *B*, The stress induction procedure increased (area under the curve) cortisol levels (expressed as percentage of baseline) (45–135 min) (*A*) and reduced mean phasic pupil dilation (expressed as ratio of baseline diameter) after the initial light reflex (*B*). Significance refers to the observed within-subject effects, and the error bars represent SEM of the between-subject variance. $*p < 0.05$.

with previous literature (Bradley et al., 2008), a significant effect of item valence was observed in pupil dilation responses, with negative pictures causing more dilation, indicating stronger phasic sympathetic responses, than neutral ones ($F_{(1,11)} = 52.08$; $p < 0.001$) (supplemental Fig. S1A, available at www.jneurosci.org as supplemental material). However, this measure did not yield any significant interaction effects between item valence and stress ($F_{(1,12)} < 1$).

Effectiveness of stress induction: psychological measures
Stress induction led to an increase in subjective stress, as measured by elevated self-reported negative affect (PANAS questionnaire) measured just before the encoding blocks (mean $\pm$ SD; $NA_{control}$, 13.97 $\pm$ 4.62; NA_{stress}, 16.08 $\pm$ 4.79; $F_{(1,17)} = 7.21$; $p = 0.02$). Picture ratings obtained during encoding blocks were highly consistent with predetermined picture categories, with 94.7 $\pm$ 0.3% corresponding (correct) responses. Whereas reaction times for (correct only) picture rating were independent of picture valence ($F_{(1,17)} < 1$), stress induced a trend toward slower reaction times (mean $\pm$ SD; $RT_{control}$, 1.39 $\pm$ 0.33 s; RT_{stress}, 1.51 $\pm$ 0.34 s; $F_{(1,17)} = 3.57$; $p = 0.08$).

Effectiveness of stress induction: memory enhancement
Memory was tested in a CR test (Dolcos et al., 2004) the subsequent day. Stress enhanced memory performance: pictures encoded during the stressful experience were more often remembered 1 d later than pictures encoded in the control condition (mean $\pm$ SD; $CR_{control}$, 69.33 $\pm$ 20.67 pictures; CR_{stress}, 75.83 $\pm$ 18.96 pictures; $F_{(1,17)} = 4.42$; $p = 0.05$). This stress effect on picture encoding did not change over time during the encoding session (as evidenced by a nonsignificant stress by encoding block interaction, $F_{(1,17)} > 1$), indicating that this stress modulation was a rather stable state during the entire scanning session. As expected, memory performance was better for negative than for neutral pictures (mean $\pm$ SD; $CR_{neutral}$, 31.19 $\pm$ 10.88 pictures; $CR_{negative}$, 41.39 $\pm$ 10.17 pictures; $F_{(1,17)} = 51.41$; $p < 0.001$) (supplemental Fig. S1B, available at www.jneurosci.org as supplemental material). However, this picture valence effect did not interact with stress induction ($F_{(1,17)} < 1$).

Brain activation maps: main effects of stress, memory, and picture valence
Imaging data were analyzed using a random effects ANOVA with stress (stress induction vs control context), subsequent memory (later remembered vs later forgotten items), and item valence (negative vs neutral pictures) as within-subject factors. Given

Table 1. Brain regions revealing significant main, interaction, or conjunction effects

Region	Coordinates			Peak T score
	x	y	z	
Main effect of subsequent memory				
Remembered > forgotten				
Middle occipital gyrus, L	−26	−68	36	6.64***
Middle occipital gyrus, R	30	−68	38	7.39***
Inferior temporal gyrus, L	−46	−62	−6	7.94***
Inferior temporal gyrus, R	54	−56	−10	8.69***
Fusiform gyrus, L	−34	−32	−20	4.46++
Fusiform gyrus, R	34	−32	−22	4.15++
Inferior parietal lobule, L	−44	−44	56	6.63***
Inferior parietal lobule, R	36	−52	56	5.31**
Inferior frontal gyrus, L	−50	34	6	8.47***
Inferior frontal gyrus, R	52	6	22	6.21***
	54	38	6	5.93***
Forgotten > remembered				
Cuneus, L	−4	−90	24	4.86*
Cuneus, R	16	−64	34	8.46***
Lingual gyrus, L	−16	−62	−4	5.74**
Middle frontal gyrus, R	38	34	34	5.04*
	28	52	22	4.87*
Main effect of stress				
Stress > control				
Superior occipital gyrus, L	−8	−94	8	5.09*
Superior occipital gyrus, R	16	−92	20	4.99*
Lingual gyrus, R	8	−72	−2	5.86***
Fusiform gyrus, L	−36	−66	−16	3.88+
Fusiform gyrus, R	28	−70	−6	5.28*
	28	−50	−2	4.88*
Inferior temporal gyrus, R	46	−48	−18	4.06++
Stress by SME interaction (negative)				
Hippocampus, R	28	−26	−8	4.29++
Forgotten > remembered during stress				
Hippocampus, R	28	−26	−8	5.01*
Stress by SME conjunction				
Remembered > forgotten and stress > control				
Inferior temporal gyrus, R	48	−52	−6	3.20†
Stress > control and forgotten > remembered				
Lingual gyrus, L	−8	−76	−6	4.21++
	−20	−62	−4	3.68+

The peak x, y, z coordinates are given in MNI152 standard space coordinates. L and R denote left and right. SME, Subsequent memory effect. *$p < 0.05$ whole-brain corrected; **$p < 0.01$ whole-brain corrected; ***$p < 0.001$ whole-brain corrected; +$p < 0.05$ small volume corrected; ++$p < 0.01$ small volume corrected; †$p < 0.05$ small volume corrected ($r = 10$ mm) centered on the maximum of the main contrast.

strong neurophysiological evidence for its involvement in memory formation and stress–memory interactions, the MTL, and more specifically, the hippocampus (Joëls et al., 2004), was our main region of interest. Furthermore, we focused on stress-induced changes in both lower- and higher-order visual processing regions, known to be modulated by vigilance (Munk et al., 1996). Therefore, data for the MTL structures and the ventral visual stream were thresholded at $p < 0.05$, small volume corrected ($r = 15$ mm). A threshold of $p < 0.05$ whole-brain corrected was applied to all other regions.

We first identified brain responses to pictures in general that were affected by stress induction. Larger responses to picture presentation for the stress induction than the control condition were found in visual areas: activation in regions of the primary visual cortex, right inferior temporal region, and fusiform gyrus, associated with higher-order visual processing and attention (Moran and Desimone, 1985; Heinze et al., 1994), was elevated by stress induction (Table 1, Fig. 3A). Second, regions supporting successful memory formation were identified. In line with previous literature of picture encoding (Brewer et al., 1998; Dolcos et al., 2004), regions displaying larger neural activity during encod-

ing of subsequently remembered than subsequently forgotten pictures were the bilateral fusiform gyrus extending into the parahippocampal region, inferior temporal gyrus, inferior frontal cortex, inferior parietal gyrus, precentral gyrus, and the middle/superior occipital lobe. Negative effects of subsequent memory were found in the cuneus, precuneus, lingual gyrus, posterior cingulate cortex, and middle frontal cortex (Fig. 3B).

As expected, brain imaging results also revealed strong main effects of item valence (supplemental Table S1, available at www. jneurosci.org as supplemental material), with encoding activity being greater for negative than for neutral items in regions associated with visual processing (including the middle occipital and middle temporal gyri) (Lang et al., 1998; Wagner et al., 1998). Additional differences in activation were observed in the amygdala, fusiform gyrus, cerebellum, brainstem, thalamus, and inferior frontal cortex; regions typically activated in tasks involving emotional processing and arousal (Phan et al., 2002). Item valence and memory effects interacted in an extended medial temporal region, which showed larger subsequent memory effects for negative than for neutral pictures, reflecting better memory performance for these items (supplemental Table S1, available at www.jneurosci.org as supplemental material). These findings are consistent with other studies concerning emotional subsequent memory effects (Dolcos et al., 2004; Dougal et al., 2007). In line with behavioral and physiological measures, however, picture valence effects did not interact with stress induction.

Brain activation maps: conjunction and interaction effects of stress and memory

To examine the main question at issue, how stress affects memory formation, we first identified those brain regions in which activity was modulated by both stress and memory formation independently (i.e., overlapping effects), leaving the actual underlying memory processes unaffected. Both factors were associated with differential activity in the primary visual cortex and inferior temporal gyrus. To ensure actual spatial overlap, conjunction analyses (using the minimum statistic compared with the conjunction null method) over the two orthogonal contrasts (Nichols et al., 2005) were performed. Activity in the primary visual cortex was significantly increased after stress induction and was negatively associated with subsequent remembrance (Fig. 3C), indicating that stress-induced activation of this region was related to less effective memory formation. In contrast, in the inferior temporal gyrus, a combined positive stress induction and subsequent memory effect was found (Fig. 3C). Enhanced activation after stress induction in this region was apparently associated with better memory formation.

Second, we investigated whether stress interacted with memory processes and thus influenced the subsequent memory effect itself. Stress induction modulated the subsequent memory effect focally in the right hippocampus (Table 1, Fig. 4A,B). Most interestingly, the observed interaction was carried by a negative subsequent memory effect in the stress induction condition: hippocampal responses to pictures were lower during encoding of subsequently remembered compared with forgotten items. To determine whether this effect was related to the observed increases in memory performance and thus could explain observed variance in stress effects on memory performance across participants, mean activity of the anatomically defined hippocampus (bilateral) was extracted (Tzourio-Mazoyer et al., 2002) and the differences in activity between the stress and control conditions were entered into regression analyses as a predictor for the difference in memory performance. The decrease in hippocampal re-

sponse to pictures predicted the stress-induced improvement in memory performance ($r = -0.615$; $p = 0.007$), providing complementary evidence that reduced hippocampal activity is related to an increase in memory performance under stress (Fig. 4*C*).

Discussion

Here we show that acute stress profoundly affected the neural correlates of memory formation, and it did so in a region-specific manner. Reduced hippocampal responses were associated with better memory formation under stress, both within and across subjects. Furthermore, in early visual areas, stress led to an increase of activity, which was accompanied by a negative subsequent memory effect, whereas stress-enhanced activation in inferior temporal regions was accompanied by a positive subsequent memory effect.

The stress induction increased both psychological stress, as indicated by elevated self-reported negative affect, and physiological stress: both activity of the HPA axis and sympathetic tonus was increased. Moreover, decreased pupil dilation responses were found, which is widely regarded as a relatively direct index of LC activity (Koss, 1986), with stimulus-locked pupil dilation reflecting a phasic LC response. During states of stress, the LC shifts toward a tonically hyperactive state, which is thought to result in a hypervigilant processing state and a concomitant decrease in stimulus-coupled phasic LC activity (Aston-Jones and Cohen, 2005). Our finding of a decreased pupil dilation response during stress, together with the slightly elevated reaction times for picture rating, support this interpretation of a stress-induced hypervigilant state of unfocussed processing.

The stress-enhanced activity in the primary visual cortex might also support the notion of such a state change. Previous studies have shown that both attentional and emotional states modulate visual processing (Wang et al., 2006; Vuilleumier and Driver, 2007) and that hypervigilance is accompanied by potentiation of sensory input (Munk et al., 1996). The widespread neocortical projections of the LC might recruit additional neural resources to process an excess of sensory information. The negative conjunction of stress and subsequent memory effects in this region might indicate that the stress-induced activation, however, is supraoptimal for memory formation and likely contains large amounts of task-irrelevant information. Because this effect in itself is not related to better memory, additional factors are necessary to explain stress-induced memory enhancement.

One possible explanation for this memory improvement may lay in stress-enhanced filtering of excess sensory information in the ventral visual stream (Kastner et al., 1998; Kastner and Pinsk, 2004). Visual-selective attention modulates the inferior temporal cortex (Moran and Desimone, 1985), and lesions in these regions lead to attentional deficits (De Weerd et al., 1999). Under conditions of low attentional selection, cortical representations of simultaneous visual stimuli interact in a mutually suppressive manner. Attentional selection of a single stimulus results in diminishment of the suppressive influence of nearby stimuli, thus providing a neural basis for filtering
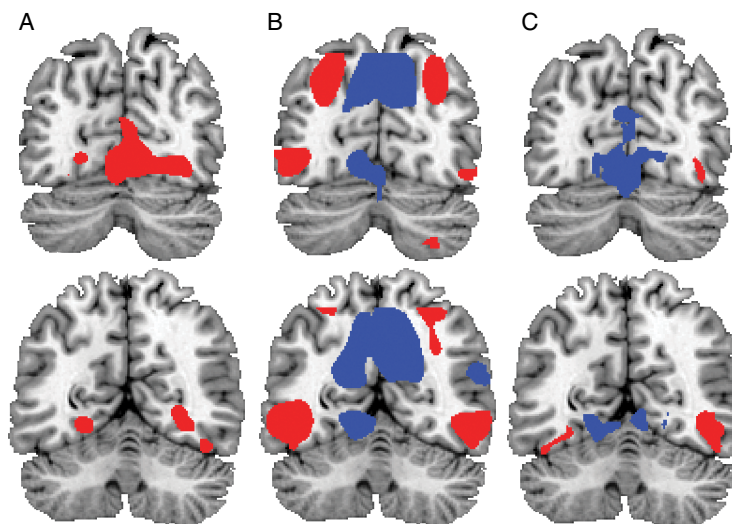

Figure 3. Brain regions affected by stress induction and memory ($y = -72, -59$). *A*, Stress induction increased responsiveness within the primary visual cortex and right inferior temporal region, centered on the fusiform gyrus. *B*, Positive (in red) subsequent memory effects in large inferior temporal and superior parietal regions and negative (in blue) subsequent memory effects in posterior midline structures comprising the cuneus and the lingual gyrus. *C*, Conjunctions of positive effects of stress induction with positive (in red) or negative (in blue) subsequent memory effects. These figures show that enhanced recruitment of the primary visual cortex after stress induction was detrimental to memory formation. In contrast, stress-enhanced inferior temporal activation proved beneficial. All statistical parametric maps are thresholded at $p < 0.001$, uncorrected, using minimum statistic/global null methods for conjunction effects, for visualization purposes. For formal statistical tests, see Table 1.

out irrelevant information (Kastner et al., 1998). Moreover, it has been proposed that tonic LC states are mirrored by increased activation of a ventral frontoparietal attention network, enhancing selective processing of salient stimuli (Corbetta et al., 2008). In line with this, we observed bilateral subsequent memory effects in these inferior temporal regions but also stress-induced activity increases. The latter can be taken to reflect reduction of ambient noise by focusing on task-relevant information. Conjunction effects of stress and subsequent memory, without interaction, indicate that activity in this region is modulated relatively independently by stress and memory formation. Thus, elevated stress may increase the likelihood of successful memory formation.

Consequently, adequate noise reduction may have led to less information relayed to the hippocampus. In line with this idea, the hippocampus showed less activity for later remembered than for later forgotten items under stress. Moreover, the overall decrease in hippocampal responses predicted the stress-related improvement in memory performance across subjects. Possibly, during stress, hippocampal input during subsequently forgotten items might be characterized by a large proportion of irrelevant information, thwarting clean separation between task-related and -unrelated information as required for the subsequent memory test. Thus, our findings suggest that stress-related memory improvements are related to a combination of increased noise reduction accompanied by, or leading to, a decreased hippocampal response.

In addition to these alterations in sensory and mnemonic operations, stress may promote a neural state optimized for memory formation. LC activation elevates hippocampal NE levels, leading to tonically increased activity (Berridge and Foote, 1991). Therefore, the level of hippocampal activity might have been generally higher during the stress compared with the control condition, but fMRI cannot detect such slowly modulated changes in baseline activity. Furthermore, corticosteroids and NE lower the threshold for synaptic modification (Groc et al., 2008). Therefore, sensitization of hippocampal plasticity, requiring less neural
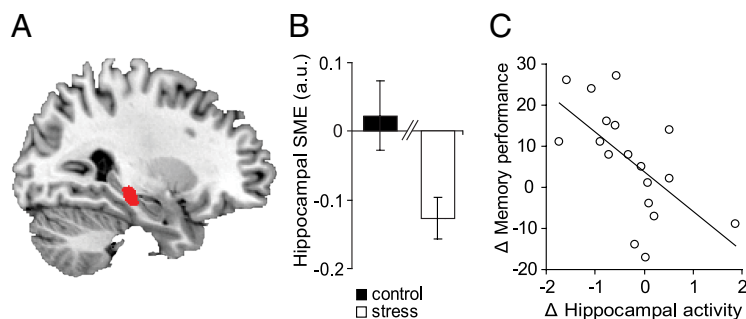
Figure 4. Stress modulated the subsequent memory effect in the right hippocampus. **A**, Statistical parametric map, here thresholded at $p < 0.001$ (uncorrected) for visualization purposes, revealed a negative stress induction by subsequent memory effect interaction ($x = 28$). **B**, Signal differences between subsequently remembered and forgotten trials separately depicted for the stress induction and control condition, based on averaged parameter estimates of the total volume of the anatomically defined hippocampus, revealed a negative subsequent memory effect during stress. **C**, The observed stress-induced decrease in hippocampal responses predicted the stress-related improvement in memory performance across subjects. Error bars represent SEM of the between-subjects variance.

input for trace formation—possibly in combination with increased baseline activity—may provide a complementary mechanism through which acute stress can enhance memory formation. However, both this tonically increased activity and sensitized plasticity would result in smaller phasic responses but cannot readily explain the observed reversal of the subsequent memory effect.

An alternative explanation for the stress-enhanced memory is that it is carried by stress effects on memory consolidation. Our memory test was deliberately delayed, precluding effects on memory retrieval (de Quervain et al., 1998; Roozendaal et al., 2006), thus creating a time window during which consolidation may have been affected. Consolidation effects have been demonstrated in studies in which stress (hormone) manipulations were restricted to the postlearning period (Oitzl et al., 2001; Andreano and Cahill, 2006; Roozendaal et al., 2006). Therefore, effects on memory consolidation are likely to have contributed to the behavioral effect observed. It appears unlikely, however, that consolidation effects were the only contributing factor, because effects of acute stress on memory encoding were evident, and individual differences in stress-induced memory enhancement were predicted by hippocampal responses during encoding.

Remarkably, our stress induction resulted in a general improvement of memory that was not specific to negative pictures. In contrast, several studies have reported interactions between picture valence and stress or cortisol (Buchanan and Lovallo, 2001; Cahill et al., 2003; Abercrombie et al., 2006; Payne et al., 2006, 2007; Roozendaal et al., 2006). This potential discrepancy may be explained by the dependence of glucocorticoid effects on simultaneous NE activation (Roozendaal et al., 2006). Previous stress induction studies have not always tested memory encoding during NE activation, because stressor and task were temporally separated. By integrating the memory task within the stress procedure, in both time and content, continuous NE activity was ensured, likely enabling glucocorticoids to affect memory for negative and neutral items.

Some limitations of the current study should be considered. First, our findings are based on a specific memory test and may therefore not generalize. However, a picture cued recall test appears quite optimal for probing emotional memory formation (Buchanan and Lovallo, 2001; Dolcos et al., 2004; Payne et al., 2006, 2007); it shows robustly the typical emotional bias effect and provides a cleaner measure of episodic memory retrieval than for instance a recognition memory test, which can be con-

founded by familiarity judgments. Furthermore, participants need to remember both the gist of the pictures (to remember the corresponding picture) and details (which determined whether the picture would be scored as recalled). Therefore, our procedure provides a useful compound measure. Nevertheless, tests specific for memory of gist as opposed to details appear important for future research (Adolphs et al., 2005). Second, we investigated men only, and, thus, we acknowledge that the obtained results cannot be readily generalized to women. The reason for excluding women was that they exhibit smaller and more variable stress responses (Kajantie and Phillips, 2006), depending on menstrual cycle phase and use of contraceptives (Kirschbaum et al., 1999; Bouma et al., 2009). In this study, however, the stress response was not of primary interest in itself but merely served as independent variable, which is why we opted to recruit the population with the most robust and stable stress response. Although important, sex- and cycle-specific effects were beyond the scope of this initial study. Third, it would have been interesting to assess also movie-related memories, but practical reasons restrained us from doing so. The clips used do not contain many distinct details that could be probed in a subsequent memory test, and movies do not allow straightforward designs with subsequent memory effects. It is also impossible to align all physical and semantic features of the stress and the control movies. Thus, stress effects would have always been confounded by irrelevant factors. Instead, we show that memory formation for pictures that are identical across participants is affected by the state the participant is in.

In conclusion, the present study demonstrates that acute stress profoundly affects the neural substrates of memory formation, and it does so in a region-specific manner. Our findings suggest that acute stress is accompanied by a shift into a hypervigilant mode of sensory processing in combination with increased allocation of neural resources to noise reduction. This reduction of task-irrelevant ambient noise, in combination with a stress-hormone-induced optimal state for neural plasticity, may explain why stressful events attain a privileged position in memory. This interpretation provides a heuristic framework for additional investigation into the mechanisms underlying trauma etiology.

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