Novel Scenes Improve Recollection and Recall of Words

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Abstract

■ Exploring a novel environment can facilitate subsequent hippocampal long-term potentiation in animals. We report a related behavioral enhancement in humans. In two separate experiments, recollection and free recall, both measures of hippocampus-dependent memory formation, were enhanced for words studied after a 5-min exposure to unrelated novel as opposed to familiar images depicting indoor and outdoor scenes. With functional magnetic resonance imaging, the enhancement was predicted by specific activity patterns observed during novelty exposure in parahippocampal and dorsal prefrontal cortices, regions which are known to be linked to attentional orienting to novel stimuli and perceptual processing of scenes. Novelty was also associated with activation of the substantia nigra/ventral tegmental area of the midbrain and the hippocampus, but these activations did not correlate with contextual memory enhancement. These findings indicate remarkable parallels between contextual memory enhancement in humans and existing evidence regarding contextually enhanced hippocampal plasticity in animals. They provide specific behavioral clues to enhancing hippocampus-dependent memory in humans. ■

INTRODUCTION

Long-term potentiation (LTP) in the rodent hippocampus is regarded as a neurophysiological, cellular model of learning and memory formation (McGaugh, 2005). Exploring a novel environment can facilitate LTP via neuromodulation, such as by noradrenergic (Straube, Korz, Balschun, & Frey, 2003) or dopaminergic inputs (Sajikumar & Frey, 2004). Remarkably, the neuromodulatory influence of novelty on synaptic plasticity occurs both during novelty exploration (Davis, Jones, & Derrick, 2004) as well as up to 30 min subsequent to exploration (Li, Cullen, Anwyl, & Rowan, 2003; Straube et al., 2003). Most interestingly, dopaminergic neuromodulation seems to be critical for these temporally extended effects. Rats allowed to move freely in a novel spatial environment subsequently had a reduced threshold for LTP induction in the hippocampal CA1 region, and this facilitation was blocked by dopamine (D1/D5) receptor antagonists but not by antagonists of noradrenergic neurotransmission (Li et al., 2003). Physiologically, these effects of dopaminergic neuromodulation could be linked to mechanisms allowing a tonic increase in hippocampal dopamine availability (Floresco, West, Ash, Moore, & Grace, 2003), which in turn may result in an increase of plasticity-related proteins required for LTP consolidation (Lisman & Grace, 2005; Sajikumar & Frey, 2004; Frey, 2001).

These temporally extended effects of novelty exploration on LTP induction in the hippocampus raise the possibility that hippocampus-dependent learning is improved in the context of novelty as compared to a context in which all stimuli are familiar. We investigated this possibility in humans in a similar experimental approach to that used in the aforementioned rodent study, which has demonstrated contextual effects of novelty exploration on LTP (Li et al., 2003). We hypothesized that free recall and recollection, both measures of hippocampus-dependent memory (Fernandez, Klaver, Fell, Grunwald, & Elger, 2002; Yonelinas et al., 2002; Duzel, Vargha-Khadem, Heinze, & Mishkin, 2001), should be enhanced if items are studied after a period of novelty exploration, whereas familiarity, which is believed to be less dependent on the hippocampus (Yonelinas et al., 2002; Duzel et al., 2001; Vargha-Khadem et al., 1997), should not be affected. Furthermore, recent functional imaging studies in humans suggest that reward-related activation of a midbrain region known to be involved in dopamine release, the substantia nigra/ventral tegmental area (SN/VTA), is associated with enhanced hippocampus-dependent consolidation (Adcock, Thangavel, Whitfield-Gabrieli, Knutson, & Gabrieli, 2006; Wittmann et al., 2005). We therefore also accounted for the possibility that such an enhancement might be detectable only if memory was tested after allowing sufficient time for consolidation (i.e., tested on the next day). This assumption

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was also motivated by animal data showing that the activation of dopamine (D1/D5) receptors in CA1 enhances consolidation of inhibitory avoidance in rats, whereas blockade of these causes amnesia (Bernabeu et al., 1997), and by the fact that dopaminergic neuromodulation is associated with the maintenance of LTP (i.e., ''late-LTP'') in CA1, a phenomenon that could possibly tap into consolidation (Sajikumar & Frey, 2004).

Successful exploration of novelty also requires directing attention toward novelty and perceptual analysis of novel information (Nyberg, 2005; Mesulam, 1998). Patients with prefrontal lesions have electrophysiological and behavioral evidence of impaired direction of attention toward novel stimuli (Daffner et al., 2000). These patients spend less time viewing images of novel objects in conjunction with a reduction in amplitude of an electrophysiological marker of novelty (Daffner et al., 2000). Perceptual analysis of images of scenes is associated with activation of the parahippocampal cortex in humans (Tong, Nakayama, Vaughan, & Kanwisher, 1998). Hence, it is conceivable that any behavioral enhancement of memory after novelty exploration should involve not only neuromodulatory regions and the hippocampus but also attention-related prefrontal areas and perceptual brain regions such as the parahippocampal cortex.

We investigated the influence of novelty exploration on hippocampus-dependent memory in two different experiments. The experimental design took into account our recent observation (Bunzeck & Duzel, 2006) of a nonspecific enhancement of recognition memory in the immediate context of novelty that appeared to be linked to perirhinal rather than hippocampal activity. In that study, the novelty of context was manipulated as a within-subject variable with a separation between the novel and the familiar context of only 6 min, thereby probably allowing the effects of novelty exposure to partly spill over to the familiarity context. We reasoned (Bunzeck & Duzel, 2006) that a specific hippocampal effect of novelty is more likely to be detected, if, as in the aforementioned animal experiments, the novelty of context was manipulated as a between-subject variable, thereby allowing a clear separation of the novel and familiar context. Furthermore, in our previous study, the memory enhancement was demonstrated for material that belonged to the same category as the one that transported novelty (images of scenes). In the present study, we used images of scenes to introduce novelty and unrelated, visually presented words to probe memory, thereby ensuring that any enhancement by novelty is not restricted to within-category processing.

The goal of the first experiment was to demonstrate the phenomenon behaviorally and assess whether it was present immediately and/or 24 hr later after novelty exploration and, moreover, to differentiate novelty-specific enhancement from that induced by emotional arousal (see Figure 1 for experimental setup). Three groups of subjects (n = 14 each) first participated in a precontext control condition (Figure 1). In the critical part of the experiment, the groups viewed novel (novelty context), familiar (familiarity context), or emotionally negative familiar (emotional context) images of scenes for 5 min. Each subject then also viewed familiar images of scenes for another 5 min ensuring, as in animals studies (Li et al., 2003), that differences in arousal between each group were minimized. After context exposure, subjects learned a list of words which they had already seen once the day before by making living/nonliving judgments on each word. Recollection and familiarity estimates (Yonelinas & Jacoby, 1995) (RE and FE) were obtained using a recognition memory test immediately after learning for half of the words and on the next day for the rest (delayed testing).

The goal of the second experiment was to replicate the findings of the first experiment using a different measure of hippocampus-dependent memory (free recall) and to utilize functional magnetic resonance imaging (fMRI) to examine whether the behavioral enhancement was related to the activation of the SN/VTA region and the hippocampus during novelty exploration as well as to the activity of prefrontal regions implicated in the direction of attention to novelty and parahippocampal cortices which are implicated in the perceptual processing of scenes (see Figure 2 for experimental setup). The short retention interval associated with the free recall test in Experiment 2 was motivated by the early improvement of memory quality in Experiment 1. Our goal with the imaging experiment was to assess what aspect of novelty exploration is most closely related to subsequent learning. Due to this reason, we did not scan during the learning phase of the word lists. Stronger SN/VTA activation to the novel than to the familiar pictures would indicate stronger activation of dopaminergic circuitry prior to word learning. We hypothesized that the amount of SN/VTA activation to novel stimuli would correlate with the free recall rate for the words presented in the same context.

METHODS

Experiment 1

Participants

Forty-two right-handed healthy adults (26 women, age = 20–30 years, normal or corrected-to-normal vision) participated after giving informed written consent and were reimbursed with €24. The study was approved by the Ethics Committee of the Otto-von-Guericke University, Magdeburg.

Stimuli

A total of 560 neutral German words of 4–10 letters were chosen from the Celex database (Baayen, Piepenbrock, & von Rijn, 1993). The words were presented in white Arial 18 font in the center of a 17-in. computer screen. Half of the words denoted living and the other half

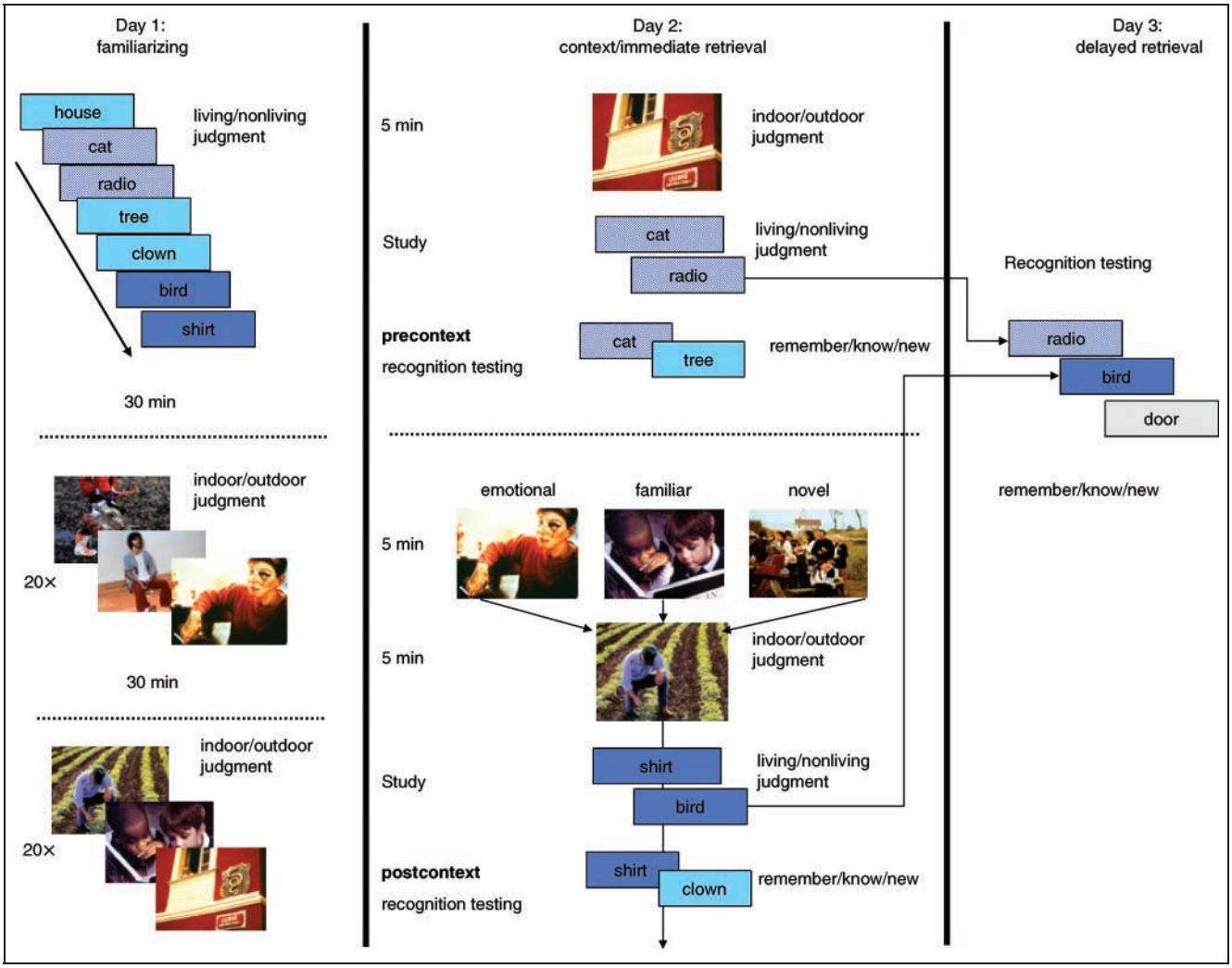

Figure 1. Experimental setup of Experiment 1. (Day 1) Familiarization with all stimuli (560 words, 12 neutral, and 12 emotional images). (Day 2) Control condition: presentation of familiar neutral images, followed by 160 familiar words and a immediate recognition memory test for 80 of these words and 80 words from the day before; context condition: presentation of either familiar neutral, familiar emotional, or novel neutral images followed by familiar neutral images followed by 160 familiar words and a memory test for 80 of these words and 80 from the day before. (Day 3) Recognition memory test for the remaining two halves (160) of the words from Day 2 and for 80 completely new words.

nonliving concepts. Images of scenes were taken from the international affective picture database (Lang, Bradley, & Cuthbert, 2001). Twelve images of emotionally negative content and 72 images of neutral content were selected. Half of the images showed indoor scenes and the other half showed outdoor scenes.

Procedure

The experiment comprised three consecutive days. On the first day, all participants were familiarized with 12 images containing emotionally negative scenes, 12 images containing neutral scenes, and 560 neutral words (Figure 1). By familiarizing each study-word, we intended to minimize novelty from the study material itself in order not to confound the contextual novelty manipulation on Day 2 with the overall novelty of the study-material. Participants first saw the 560 words and had to make a living/nonliving judgment on each word by pressing one of two corresponding mouse-buttons with the right index and middle fingers. The words were presented for 1 sec followed by the presentation of a fixation cross for 2 sec. After studying all words, participants were administered one of the two parallel versions (BF-S and BF-S′) of a mood inventory (Zerssen & Koeller, 1976) and the German version of the state questionnaire of the State–Trait Anxiety Inventory (Laux, Glanzmann, Schaffner, & Spielberger, 1981). Thirty minutes after studying all words, the emotional images were presented. Participants made an indoor/outdoor judgment on these images by pressing one of two corresponding mouse-buttons with the right index and middle fingers. The images were repeated 20 times and each picture was presented for 3 sec followed by 2 sec fixation. After the presentation of the emotional images, there was another delay of 30 min in which participants filled in the second parallel version of

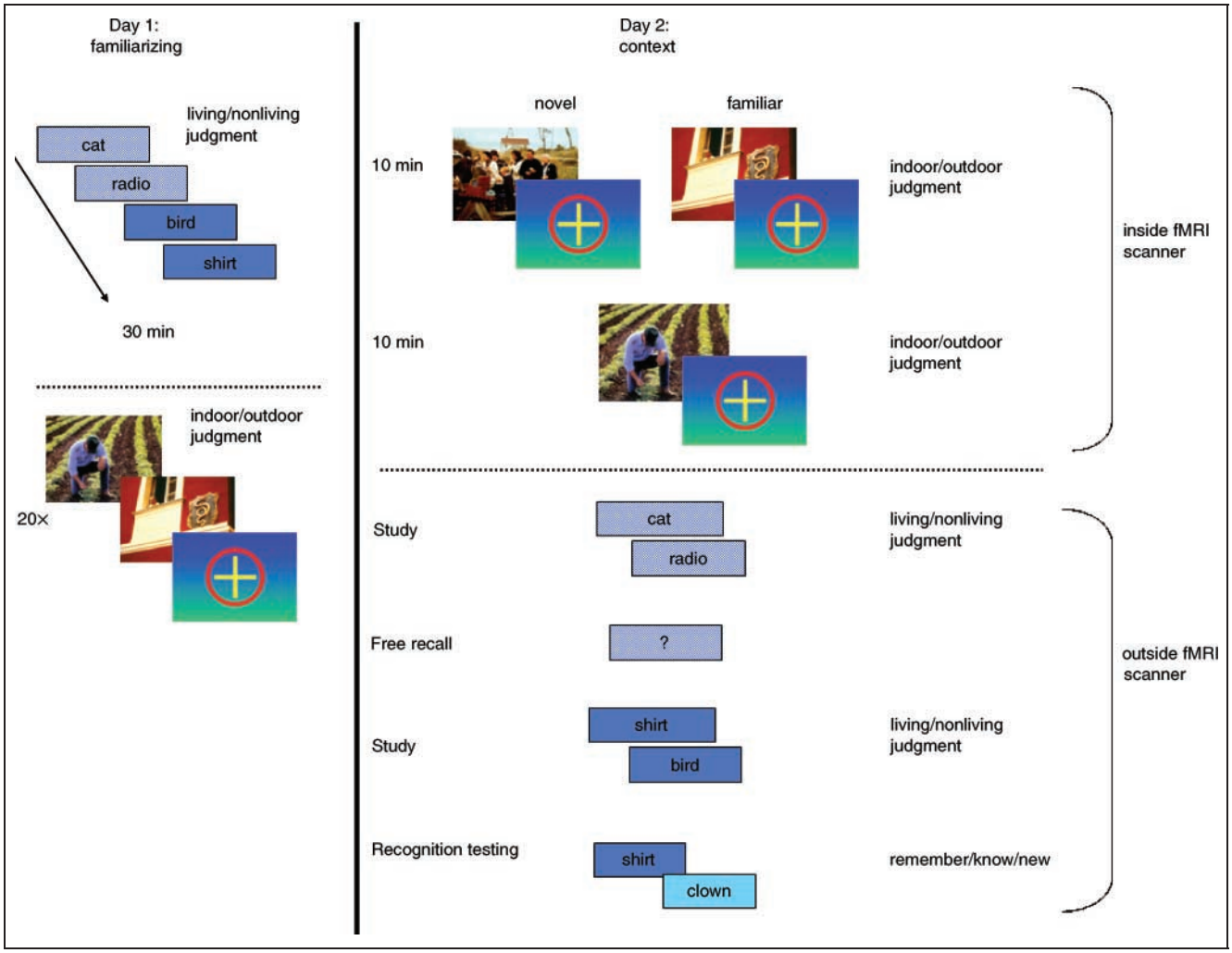

Figure 2. Experimental setup of Experiment 2. (Day 1) Familiarization with all stimuli (200 words presented once, 8 neutral images and two types of fixation images presented 20 times). Day 2 in the fMRI scanner, context presentation of either familiar neutral (n = 16) or novel neutral (n = 15) images intermixed with fixation images, followed by neutral familiar images and fixation images. Then, outside the fMRI scanner, this was followed by five study-recall blocks. Each block had a study list of 20 familiar words (from the day before) followed by a postdistraction free recall test. The study-recall blocks were then followed by a study-recognition block. Here, a study list of 100 familiar words (from the day before) was presented for learning. This was followed by a recognition memory test for these words together with 100 new distracter words.

the mood inventory and the trait anxiety inventory. Finally, the 12 neutral images were presented, again repeated for 20 times with the same timing and task as the emotional images. On Day 2, all subjects first participated in a ''precontext/control condition'' during which they ''explored'' a subset of four familiar/emotionally neutral images for 5 min for which they had to provide an indoor/outdoor judgment again. Each picture was presented for 3 sec followed by 2 sec fixation. After the images, a set of 160 familiar words were shown and participants had to make living/nonliving judgments for each word (see Table 1 for reaction times [RTs] and accuracy). They were told that their memory for the words would be tested later. As on the day before, each word was shown for 1 sec followed by 2 sec fixation. Immediately following the study list, recognition memory for half (80) of the words was tested using the remember/know procedure (Duzel, Yonelinas, Mangun, Heinze, & Tulving, 1997). Studied words were randomly intermixed with 80 ''distractor'' words from the day before. For each word (1 sec presentation followed by a 3-sec fixation cross), participants made a three-choice button response indicating if it was not part of the study list (''new,'' left index finger), or if it was part of the study list whether they recollected a particular aspect of the study episode (''remember'' responses, right index finger) or just knew that the word was studied because of a strong feeling of familiarity (''know'' responses, right middle finger) in the absence of any recollection. Response classes were ''new'' responses to unstudied words (correct rejections, CR), ''remember'' responses to unstudied words (remember/false alarm, rem/fa), ''know'' responses to unstudied words (know/false alarm, know/fa), ''remember'' responses to words studied (remember, rem.), ''know'' responses to words studied (know), and finally, ''new'' responses to words studied (miss) (Table 1).

Table 1. Reaction Times and Response Accuracy at Encoding, and Response Frequencies at Retrieval (Experiment 1)

Condition	*Context*	*RT*	*AC*
Encoding			
Precontext encoding	emo.	917 (272)	94% (2%)
	fam.	954 (278)	93% (4%)
	nov.	865 (217)	90% (10%)
Postcontext encoding	emo.	952 (289)	88% (12%)
	fam.	992 (286)	85% (15%)
	nov.	931 (210)	86% (16%)

Condition	*Context*	*Rem.*	*Know*	*Miss*	*CR*	*Rem/fa*	*Know/fa*
Immediate Recognition Testing/Learning Performance							
Precontext/control	emo.	42% (13%)	33% (13%)	25% (14%)	79% (8%)	6% (4%)	15% (7%)
	fam.	38% (15%)	33% (14%)	28% (14%)	80% (12%)	5% (8%)	15% (10%)
	nov.	41% (23%)	29% (20%)	30% (18%)	77% (13%)	7% (6%)	16% (12%)
Critical context	emo.	34% (18%)	39% (17%)	27% (16%)	82% (9%)	4% (5%)	13% (16%)
	fam.	28% (15%)	39% (16%)	32% (19%)	81% (12%)	3% (4%)	17% (19%)
	nov.	40% (23%)	29% (19%)	31% (19%)	78% (13%)	6% (6%)	15% (19%)
Delayed Recognition Testing/Consolidation							
Precontext/control	emo.	25% (18%)	37% (17%)	38% (14%)	83% (12%)	4% (7%)	13% (9%)
	fam.	17% (11%)	42% (18%)	40% (19%)	85% (10%)	1% (1%)	13% (10%)
	nov.	33% (18%)	33% (15%)	41% (19%)	81% (11%)	3% (3%)	15% (10%)
Critical context	emo.	24% (17%)	38% (15%)	38% (15%)	83% (12%)	4% (7%)	13% (9%)
	fam.	16% (10%)	40% (15%)	44% (17%)	85% (10%)	1% (1%)	13% (10%)
	nov.	30% (19%)	33% (13%)	37% (16%)	81% (11%)	3% (3%)	15% (10%)

Mean reaction times (RT) and accuracy (AC) collapsed over living/nonliving judgments at the two encoding sessions for the three different context groups (emo. = emotional; fam. = familiarity; nov. = novelty). Relative mean frequencies of all response classes for immediate and delayed recognition memory testing in the control and the critical context conditions, and for the three context groups. Rem = remember responses; CR = correct rejections; rem/fa = remember responses to new words (remember false alarm rates); know/fa = know responses to new words (know/false alarm rates). The numbers in brackets refer to standard deviations. Note that in the delayed recognition testing, CR and fa for the precontext control and the critical context condition are the same because they were obtained from the same distracters.

After the control condition, participants were randomly assigned to one of the three different context groups (emotional, familiarity, novelty) for the critical context condition, resulting in 14 participants per group. In the emotional-context group, participants explored a set of four familiar emotional images repeated for 5 min (total of 60 stimuli); in the familiarity-context group, they explored a set of four familiar neutral images repeated for 5 min (total of 60 stimuli); and in the novelty-context group, they saw 60 novel images which were also shown over 5 min. To minimize any differences in arousal levels between the three groups, all participants then had to explore familiar/emotionally neutral images of scenes for another 5 min (see also Li et al., 2003) (total of 60 stimuli). The picture presentation was followed by another study list of 160 familiar words (see Table 1 for RTs and accuracy) and a recognition memory test for half of the words. The timing of stimulus presentation and task instructions was the same as in the control condition. Finally, on the third day, recognition memory (remember/know procedure) was tested for the remaining 80 words from the control condition, the remaining 80 words from the experimental condition, and 80 completely new words. The time of the retrieval (immediate vs. delayed to the next day) and the condition (precontext/control vs. critical context) for a given word was counterbalanced over all subjects.

Behavioral data from the remember/know recognition memory test (Table 1) were used to obtain recollection estimates (RE) and familiarity estimates (FE) on

the basis of a model (Yonelinas, Dobbins, Szymanski, Dhaliwal, & King, 1996) of human (Yonelinas et al., 2002) and rodent (Fortin, Wright, & Eichenbaum, 2004) memory according to which recollection represents a hippocampus-dependent threshold process, whereas familiarity represents a signal-detection process that can be supported in the absence of an intact hippocampus (Yonelinas et al., 2002; Duzel et al., 2001). According to this model, recollection is the proportion of correctly recollected items (correct remember responses) that exceed a threshold (remember/false alarms, RFA), hence, can be estimated by subtracting RFA from correct remember responses. Familiarity, on the other hand, is a signal-detection process and its estimation in the remember/know procedure needs to take into account that remember and know are mutually exclusive responses. Familiarity is estimated by first calculating familiarity responses (FR) which is the ratio of the difference of the overall hit rate (i.e., remember plus know responses) and the RE divided by 1 minus the RE, and then looking up the corresponding d' value by considering FR and the overall false alarm rate (see formula below).

$$\mathrm{FR} = \frac{(\mathrm{hitrate} - (\mathrm{rem} - \mathrm{RFA}))}{1 - (\mathrm{rem} - \mathrm{RFA})} = \frac{\mathrm{hitrate} - \mathrm{RE}}{1 - \mathrm{RE}}$$

In order to be able to compare estimates of recollection (RE), which are response proportions in percent, and familiarity (FE), which is a d', both measures were transformed into z-scores before statistical analyses applying analysis of variance (ANOVA). The z-scores were based on the mean and the standard deviation (of RE and FE, respectively) of each recognition test (i.e., immediate retrieval: precontext, postcontext; delayed retrieval: precontext, postcontext) collapsed over all three context groups. Group differences were analyzed on the basis of these z-scores using ANOVA. The post hoc comparisons involved additionally the real values of RE and FE.

Experiment 2

Participants

Thirty-two participants (20 women, age 20–35 years) took part in the experiment after giving informed written consent and were reimbursed with €24. The study was approved by the Ethics Committee of the Otto-von-Guericke University, Magdeburg.

Stimuli

Three hundred neutral German words of 4–10 letters, which have been used in Experiment 1, were selected. The words were presented in white Arial 18 font in the center of a 17-in. computer screen. Half of the words denoted living and the other half nonliving concepts. Sixty-eight images from the 72 neutral images of Experiment 1 were chosen. Half of the images showed indoor scenes and the other half showed outdoor scenes. Additionally, two types of different fixation images were created. These images either depicted a cross located completely inside a circle or a cross of which the horizontal bar was partly outside of the circle.

Procedure

The experimental setup comprised two consecutive days (Figure 2). The familiarization phase on Day 1 was similar as in Experiment 1, but differed in terms of stimulus numbers and types (see above).

On the first day, participants were familiarized with the 200 neutral German words, eight neutral images half of which depicted indoor and the other half depicted outdoor scenes, and two different types of fixation images (inside/outside). The inside images depicted a cross located completely inside a circle and the outside images depicted the cross of which the horizontal bar is partially outside of the circle. The task for the words was to make a living/nonliving judgment and for the images to make an indoor (inside)/outdoor (outside) judgment. The timing of the word and picture presentation was identical to Experiment 1. The images were also repeated for 20 times. Between the presentation of the words and the images and after the picture presentation, participants filled in the same questionnaires as in Experiment 1 to allow for the same timing.

On the second day, participants were divided in two different groups (novelty- and familiarity-context group), resulting in 16 participants per group. In the fMRI scanner, participants in the novelty-context group were presented a set of 60 novel neutral images (30 depicting indoor scenes and 30 depicting outdoor scenes) and the fixation images (inside/outside) from the day before (repeated for 15 times, resulting in 60 images). The images were presented for 3 sec each. The interstimulus interval (ISI) was jittered between 3.75 and 6.75 sec with steps of 1.5 sec (mean ISI 5 sec), resulting in a run length of 10 min and 120 trials. After that, in the second run, a set of four familiar images and the fixation images were repeatedly presented for 15 times, resulting in 120 images. The timing was the same as in Run 1. Participants had to provide an indoor (inside)/outdoor (outside) judgment in both runs. Participants in the familiarity-context group were presented with another set of four different familiar images and fixation images in Run 1 followed by the familiar images in Run 2. The task was the same as in the novelty-context group. After scanning, participants studied 100 familiar words (from the day before) in 5 blocks of 20 words each outside the scanner. The words were shown one after the other for 1 sec each followed by a 2-sec fixation cross. For each word they had to provide a living/nonliving judgment via button press. Each block of 20 words

was followed by a distractor task: Participants decided via button press whether the given solution for each of four arithmetic problems (additions of two numbers) was correct. Each arithmetic problem was shown for 4 sec. After the distractor task they were prompted to freely recall within 90 sec as many of the previously shown 20 words as possible. Their responses were recorded on-line by the experimenter. After 5 blocks of the free recall test, the remaining 100 familiar words were shown for 1 sec each followed by 2 sec fixation for a living/nonliving judgment. This was followed by the distractor task (arithmetic problems) and, finally, by a recognition memory test for the 100 words using the remember/know task (see Procedure section of Experiment 1). Participants were shown the 100 old words and 100 new words. Each word was presented for 1 sec followed by 3 sec fixation cross. For each word, they had to provide their response via button press. The words were counterbalanced over the two different testing conditions (free recall and recognition). Group differences were analyzed using ANOVAs.

Image Acquisition

The functional images were acquired on a 3-T whole-body MRI system (Siemens Magnetom Trio, Erlangen, Germany) with echo-planar imaging (EPI) using an eight-channel head coil. The slices were acquired parallel to the brainstem in an odd–even interleaved direction. In the functional session, 24 T2*-weighted echo-planar images per volume, with blood oxygenation level-dependent (BOLD) contrast, were obtained (matrix: 64 × 64; 24 slices per volume; field of view (FOV): 192 × 192 mm; spatial resolution: 3 × 3 × 3 mm; gap = 0.3 mm; TE = 30 msec; TR = 1500 msec; flip angle = 75°). These partial volumes covered the hippocampus, amygdala, brainstem (including diencephalon, mesencephalon, pons, and medulla oblongata), and parts of the prefrontal cortex. For each subject, functional data were acquired in two scanning sessions containing 412 volumes per session. Six additional volumes per session were acquired at the beginning of each functional session and were subsequently discarded form the analysis to allow for steady state magnetization. Images of each subjects entire brain were collected by T1-weighted inversion recovery prepared EPI (IR-EPI) sequences (matrix: 64 × 64; 60 slices; FOV: 192 × 192 mm; spatial resolution: 3 × 3 × 3 mm; gap = 0.3 mm; TE = 33 msec; TI = 1450 msec; TR = 1500 msec). To further verify the anatomical properties of the midbrain, additional magnetization transfer (MT) images of 33 subjects were acquired (matrix: 256 × 256; 48 slices; FOV: 250 × 250 mm; spatial resolution: 0.98 × 0.98 × 3 mm; TE = 20 msec; TR = 26000 msec; flip angle = 90°) to create a MT template (Bunzeck & Duzel, 2006) (see below). The fMRI data were preprocessed and statistically analyzed by the General Linear Model approach using SPM2 software package (Wellcome Department of Cognitive Neuroscience, University College, London, UK) and MATLAB 7 (The Mathwork, USA). All functional images were corrected for odd/even slice intensity differences with reference to the middle slice acquired in time, corrected for motion artifacts by realignment to the first volume, and spatially normalized to a standard T1-weighted SPM template. The normalization was realized by warping the subjects anatomical IR-EPI to the SPM template and applying these parameters to the functional images. The images were resampled to 2 × 2 × 2 mm and smoothed with an isotropic 4-mm full-width half-maximum Gaussian kernel. The time-series fMRI data were high-pass-filtered (cutoff 120 sec) and globally scaled over voxels and scans within each session. A statistical model for each subject was computed by applying a canonical response function. To capture residual movement-related artifacts, six covariates per session were included (the three rigid-body translations and three rotations determined from initial coregistration).

MT images

To localize midbrain activity for the two-sample *t* test, the activation maps were superimposed on an MT template (Bunzeck & Duzel, 2006) (Figure 3B). This was derived by averaging 33 individual MT images after they were spatially normalized to the standard MNI template supplied by SPM99 (Bunzeck & Duzel, 2006). The substantia nigra (SN) can be easily distinguished from surrounding structures on MT images as a bright stripe (Bunzeck & Duzel, 2006). All SPM results are shown in neurological convention and the coordinates are given in MNI (Montreal Neurological Institute) space.

Analysis of Imaging Data

Regionally specific condition effects were tested by employing linear contrasts for each subject and different conditions (novel picture minus fixation baseline and familiar picture minus fixation baseline for the first run only, respectively, for the two groups). The resulting contrast images were submitted to a second-level analysis. Here, a two-sample *t* test was used on images obtained for each subjects' volume set and different conditions. Given our a priori hypotheses, the results were thresholded at a *t* value of 2.8 ($p < .005$) and a cluster size (k) = 100 voxels, respectively. Based on the averaged MT images of 33 subjects, we assessed the activation within the SN and the hippocampus for novelty. Within these regions, we extracted the contrast values of each individual participant of the first-level analysis separately for each group (novel picture minus fixation baseline and familiar picture minus fixation baseline of the first run, respectively) by applying a sphere with a radius of 4 mm over the local maxima of the two-sample *t* test (region-of-interest analysis, ROI). These values were then used to plot (Figure 3D, E, F) and

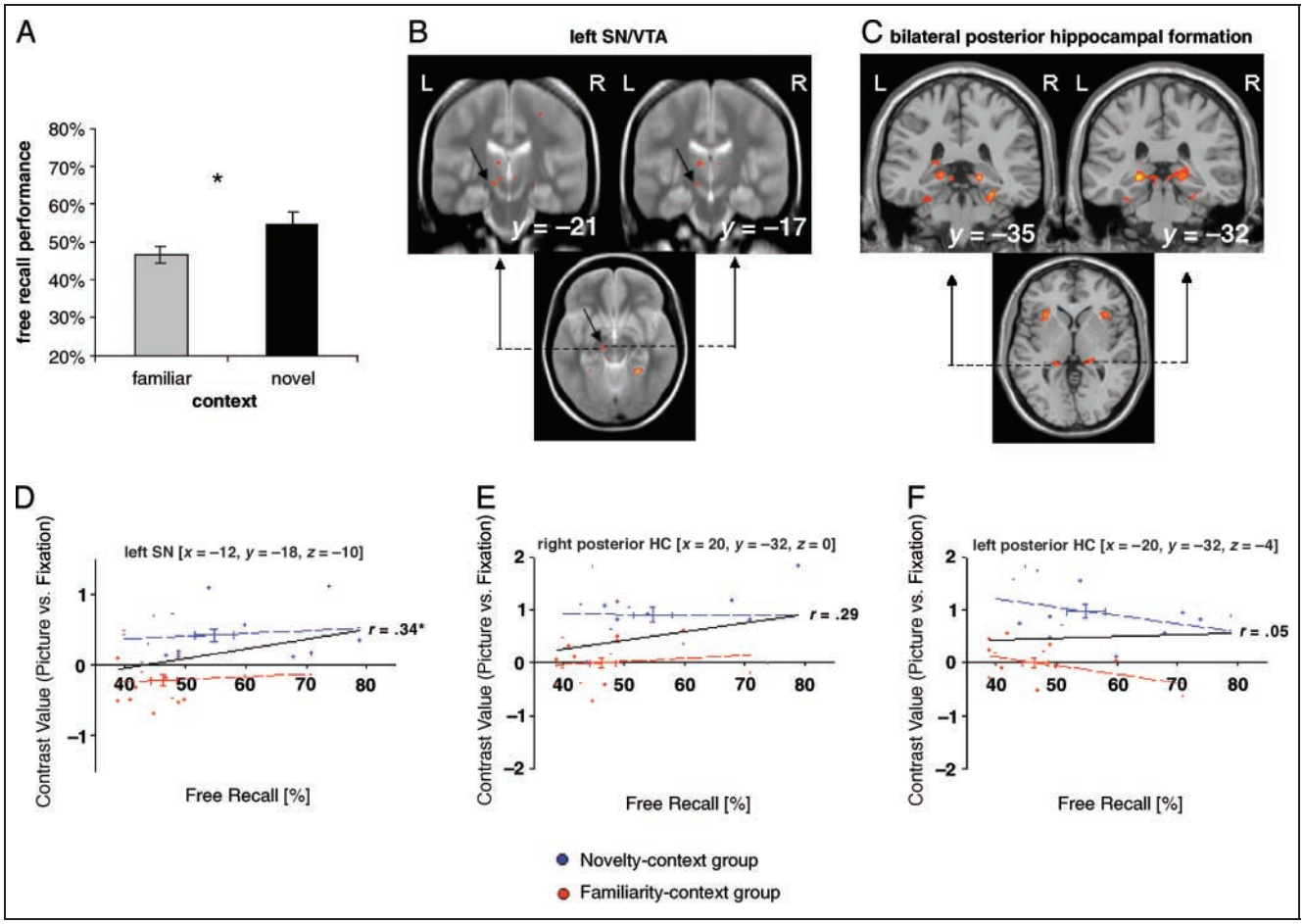

Figure 3. Behavioral performance and fMRI findings of Experiment 2. Upper row: (A) Free recall performance of the novelty- and the familiarity-context groups. The bars refer to group means, the error bars to the standard error of the mean (*SEM*), and the asterisks to statistically significant differences. (B and C) Two-sample *t* test of novelty context versus familiarity context shows higher (SPM group analyses, $p < .005$, $k = 100$ voxels) activity in the novelty context in the left substantia nigra (SN)/ventral tegmental area (VTA), and bilateral posterior hippocampal formation. Lower row: Scatterplot and correlation of contrast values from first-level analysis and free recall performance in the left (D) SN/VTA. (E and F) Scatterplots of contrast values from first-level analysis and free recall performance in the bilateral posterior hippocampal formation. Horizontal bars refer to *SEM* for free recall performance, vertical bars refer to *SEM* of contrast values, the blue and red dashed lines are the regression lines for the novelty-context and familiarity-context group, respectively, whereas the black solid line is the regression line over all subjects, and finally, the *r*s (in corresponding colors to the lines) refer to the Pearson's correlation coefficient. The asterisks denote statistically significant correlations.

calculate the correlation between regional activity and later free recall performance.

Additionally, for an unbiased assessment of the correlation of free recall performance on contextual activation, the individual free recall values were entered as a regression in the SPM analysis of participants' contrast images (i.e., contrast images of novel images minus fixation baseline and familiar images minus fixation baseline of the first run, respectively). These images were thresholded at a *t* value of 2.8 ($p < .005$) and $k = 50$ voxels (we applied the smaller cluster size because we expected the size of correlated activation not to be as extended as the size of novelty related activations). The resulting SPM activation maps provided ROIs (4 mm sphere over the local maxima) for a further correlation of extracted contrast values and free recall performance (Figure 4C and D). All SPM results are shown in neurological convention and the coordinates are given in MNI space. All correlation coefficients provided refer to Pearson's *r*.

RESULTS

Experiment 1

We calculated separate ANOVAs to investigate the effect of the different contexts during encoding and retrieval. Context (emotional vs. novel vs. familiar) had no effect on RTs or response accuracy in the living/nonliving judgments (i.e., encoding) [all Fs$(1, 26) < 1$, ps $> .1$]. RTs slowed down from the pre- to the postcontext encoding session [Fs$(1, 26) > 6.00$, all ps $< .05$] regardless of the context [$F(1, 26) < 1$, $p > .1$], suggesting increasing fatigue in the course of the experiment (Table 1).

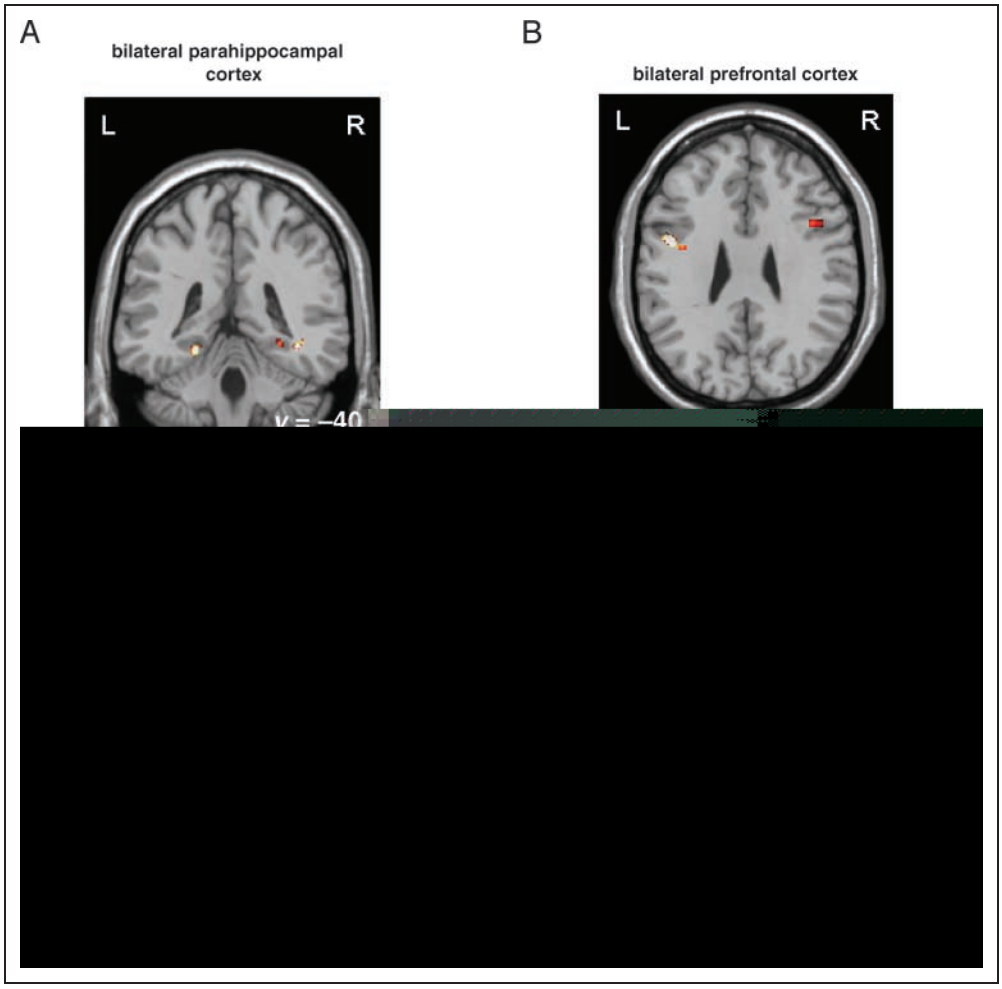

Figure 4. SPM contrast images ($p < .005$, $k = 50$ voxels) and scatterplots. Upper row: Regression analyses of free recall performance and novelty-context activation. Significant activation was found in (A) the bilateral parahippocampal cortex and (B) the bilateral prefrontal cortex. Lower row: Scatterplots of individual contrast values and free recall performance: (C) for the left parahippocampal cortex and (D) for the left prefrontal cortex. Horizontal bars refer to the *SEM* for free recall performance, vertical bars refer to *SEM* of contrast values, the blue and red dashed lines are the regression lines for the novelty-context and familiarity-context group, respectively, whereas the black solid line is the regression line over all subjects, and finally, the *r*s (in corresponding colors to the lines) refer to the Pearson's correlation coefficient. The asterisks denote statistically significant correlations.

We analyzed the retrieval data in two steps. First, to assess the effect of context on memory performance, an ANOVA involving the factors ''context'' (novelty, familiarity, and emotional), ''time relative to context exposure'' (pre- vs. postcontext presentation; for the postcontext presentation, retrieval data were collapsed over immediate and delayed testing; for the precontext presentation/control condition, data only from the immediate testing were considered as this preceded any exposure to the critical context conditions), and memory quality (recollection estimates [RE] and familiarity estimates [FE]) was calculated. This showed a three-way interaction of the factors ''context'' (novelty, familiarity, and emotional), ''time relative to context exposure'' (pre- vs. postcontext presentation), and memory quality [$F(2, 39) = 3.19$, $p = .05$]. Post hoc t tests confirmed that the RE difference between pre- and postcontext exposure (collapsed over delay) was higher in the novelty-context than the familiarity-context group; (Figure 5A; see Table 2 for individual values) [$t(26) = 2.06$, $p = .05$, two-tailed] while there was no such effects for the emotional-context group compared to the familiarity-context and novelty-context groups (Table 2, ps $> .05$) and for the FE data (Table 2, ps $> .1$).

The second step was to clarify whether this improvement of memory quality was selective to consolidation. To that end, we conducted an ANOVA on the factors ''context'' (novelty vs. familiarity), ''memory quality'' (RE vs. FE), and ''time'' (immediate vs. delayed day) considering the postcontext data only. A selective effect of consolidation would have been apparent in a three-way ''Context'' × ''Memory quality'' × ''Time'' interaction, however, there was only a significant ''Context'' × ''Memory quality'' interaction [$F(1, 26) = 6.59$, $p = .01$], but no other interactions (ps $> .1$). These data suggest that the effect of novelty context was not selective to consolidation and may have already affected encoding processes at the study phase.

Given that the novelty context was introduced during the consolidation of words studied in the precontext/control condition, we used a t test involving words studied before context exposure (in the precontext/control condition) but retrieved on the next day (delayed z-scores RE minus z-scores FE difference for words from the precontext/control condition in the novelty vs. the familiarity context) to further analyze the effect of novelty context on consolidation. This t test was significant [$t(26) = 2.33$, $p = .02$, two-tailed] (Figure 5B),

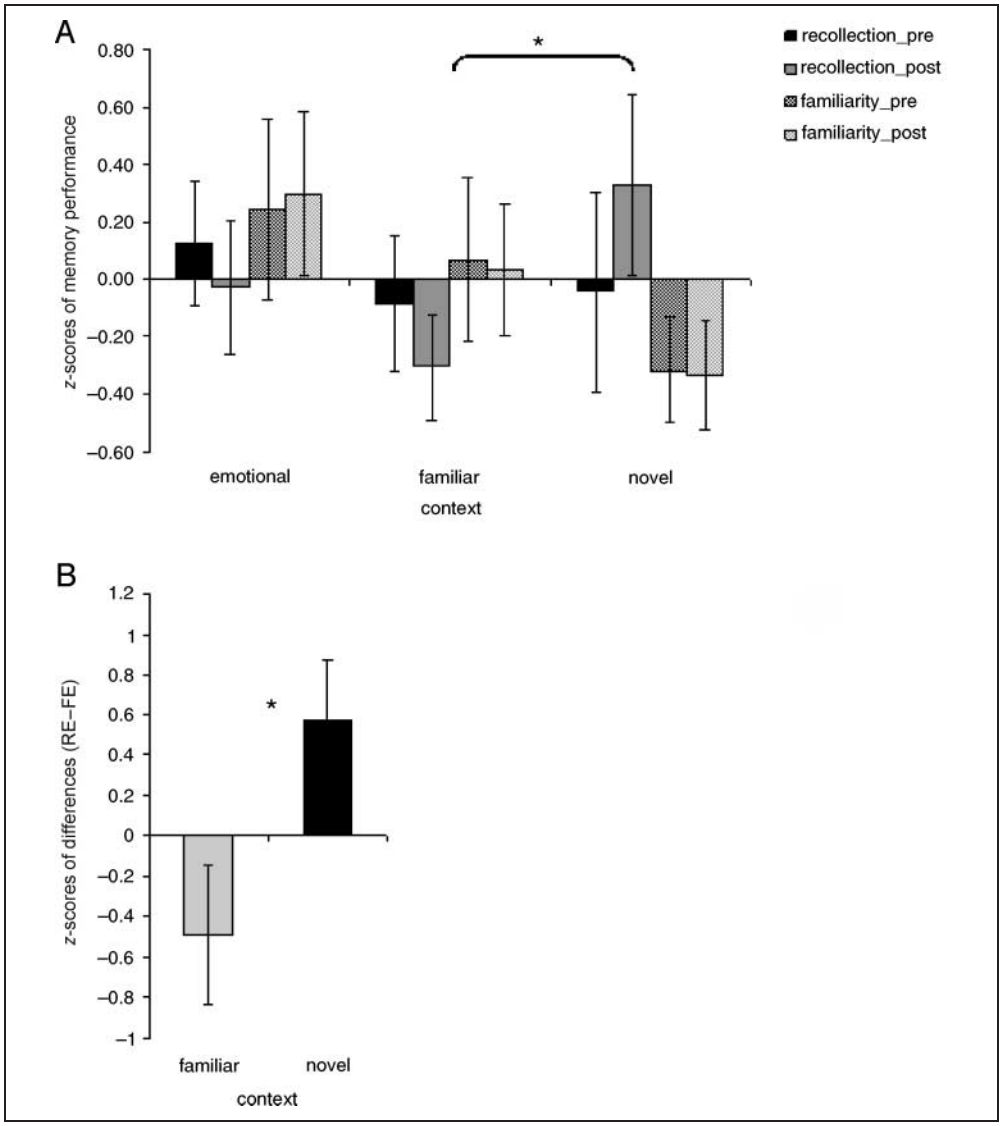

Figure 5. Recollection and familiarity estimates from Experiment 1. (A) Pre- versus postcontext testing (collapsed over immediate and delayed test) for all three contexts; (B) difference between recollection and familiarity estimates (*z*-scores of RE–FE) at delayed recognition testing of words from the control context presented before novelty and familiarity context, respectively. The bars refer to the mean *z*-scores ± 1 *SEM* (standard error of the mean). The brackets and the asterisks refer to statistically significant differences.

suggesting that the novelty context enhanced the consolidation of words already encoded into memory.

We also assessed the possibility that the different proportions of distractor items in the recognition memory tests (50% in the immediate and 30% in the delayed context) might have led to different response biases in the immediate and delayed tests and that such differences in response bias might have interacted with context. To that end, we calculated an ANOVA over the correct rejection rates of the immediate (collapsed over precontext and postcontext) and the delayed testing, using context groups as between-subjects variable and time of testing as within-subjects variable. The results show that correct rejection rate was higher in the delayed testing (mean: 83%, SEM: 2%) than in the immediate testing (mean: 79%, SEM: 2%), with a significant main effect of the factor time [$F(1, 39) = 7.01$, $p = .01$]. Importantly, however, there was neither a significant main effect of factor group nor a significant interaction between group and delay. Thus, although participants were more conservative in their responses in the delayed than the immediate testing, such a criterion shift could not have contributed to our findings regarding the effect of novelty context.

Experiment 2

A higher proportion of studied words was correctly recalled (Table 3) in the novelty-context group than in the familiarity-context group [$t(29) = 2.17$, $p = .04$; two-tailed] (Figure 3A). As in Experiment 1, this improvement occurred in the absence of differences in the accuracy and speed (RT) of living/nonliving judgments on the words during study (ps $> .3$; two-tailed) (Table 3), again making it unlikely that the improvement was related to overall arousal. However, participants were faster in the study phase of the recognition memory experiment in the novelty context in contrast to familiarity context [$t(29) = -2.24$, $p = .03$; two-tailed] (Table 3), suggesting to higher arousal (or less fatigue)

Table 2. Memory Improvement (Experiment 1)

Context	*Postcontext Minus Precontext: RE*	*Postcontext Minus Precontext: FE*
Emotional	−25%	−26%
	−21%	−24%
	−20%	−23%
	−20%	−17%
	−19%	−14%
	−15%	−14%
	−14%	−10%
	−9%	−9%
	−9%	−6%
	−9%	−5%
	−8%	−4%
	−8%	−1%
	−2%	10%
	0%	14%
	−13% (2%)	**−9% (4%)**
Familiar	−30%	−39%
	−26%	−21%
	−20%	−19%
	−17%	−18%
	−16%	−15%
	−15%	−13%
	−15%	−10%
	−14%	−7%
	−11%	−5%
	−10%	−4%
	−9%	0%
	−6%	4%
	−5%	7%
	9%	16%
	−13% (3%)	**−9% (4%)**
Novel	−29%	−29%
	−21%	−20%
	−18%	−13%
	−10%	−13%
	−9%	−11%
	−9%	−10%
	−8%	−6%
	−7%	−5%
	−5%	5%
	−2%	5%
	3%	7%
	6%	7%
	8%	8%
	9%	22%
	−7% (3%)	**−4% (4%)**

Differences between memory performance during precontext immediate recognition memory test and postcontext (collapsed over immediate and delayed testing) for recollection and familiarity estimates (RE and FE) sorted in increasing order. The percentages denote proportions of corrected remember (remember responses to old words minus remember responses to new words, RE) and know (know responses to old words minus know responses to new words, FE) responses. The values in the table show the difference between post- and precontext testing [postcontext (collapsed over immediate and delayed testing) minus precontext (immediate testing)]. The numbers in bold refer to the mean and standard errors of the mean (in brackets). Negative values refer to memory decline; positive values refer to memory improvement from the precontext to the postcontext tests.

in the second encoding session of the novelty-context group.

Following the free recall part of Experiment 2, around 25 min after context exposure, subjects also studied another list of words for which memory was tested 20 min later using the same procedure to assess memory quality as in Experiment 1. However, this time there was no selective improvement of RE but a tendency for a nonselective improvement of overall recognition memory in the novelty context [$F(1, 29) = 3.48$, $p = .07$].

It should be noted that in Experiment 1 overall memory performance for the word list after the critical context condition was lower than for the first word list presented after the control context. This was expected and most likely reflects fatigue caused by the extensive testing associated with the control condition. Note that in Experiment 2, where the critical context condition was not preceded by a control condition, we did find an absolute improvement of recall after the novelty context.

Assessment of Mood in Experiments 1 and 2

In Experiment 1, there was a significant difference of the mood ratings between before and after emotional picture exposure [$t(41) = 3.27$, $p = .01$, two-tailed], indicating that participants' mood was more negative after they viewed the emotional images. This was independent from participants' general trait anxiety as there was no correlation between trait ratings and mood change [Pearson's $r(42) = -.12$, $p = .48$; two-tailed]. That is, participants' mood ratings after the exposure to the emotional stimuli were induced by these stimuli and did not depend in their individual anxiety trait. In

Table 3. Reaction Times and Response Accuracy at Encoding; Free Recall Performance and Response Frequencies at Retrieval (Experiment 2)

Condition	*Context*	*RT*	*AC*
Encoding			
Encoding (free recall)	fam.	1142 (258)	94% (4%)
	nov.	1070 (161)	95% (3%)
Encoding (recognition)	fam.	1062 (118)	93% (2%)
	nov.	914 (230)	84% (4%)

Condition	*Free Recall*	*Rem.*	*Know*	*Miss*	*CR*	*Rem/fa*	*Know/fa*
Immediate Free Recall and Recognition Testing							
Fam.	45% (9%)	41% (21%)	38% (16%)	20% (17%)	81% (17%)	6% (11%)	13% (11%)
Nov.	55% (12%)	42% (21%)	43% (19%)	15% (11%)	87% (12%)	1% (3%)	12% (10%)

Mean reaction times (RT) and accuracy (AC) collapsed over living/nonliving judgments at the two encoding sessions for the two different context groups (fam. = familiarity; nov. = novelty). Relative mean frequencies of free recall and all response classes for the two context groups (fam. = familiarity; nov. = novelty). Rem. = remember responses; CR = correct rejections; rem/fa = remember–false alarms; and know/fa = know–false alarm responses. The numbers in brackets refer to standard deviations.

Experiment 2, there was no significant difference of mood ratings between before and after exposure to the scene images [$t(30) = -1.37$, $p = .18$, two-tailed], indicating that participants' mood did not change after viewing them.

fMRI Data in Experiment 2

fMRI data acquisition during context exposure in Experiment 2 built upon our previous work showing that the SN/VTA is activated by the novelty of images of scenes or faces rather than their negative emotional valence, rareness, or targetness (Bunzeck & Duzel, 2006). The acquisition was optimized for recording midbrain signals (Bunzeck & Duzel, 2006) but also covered the parahippocampal cortices and the dorsal portions of the prefrontal cortex, including regions where lesions impaired directing attention toward novelty (Daffner et al., 2000). Group contrasts (2-sample t test between the novelty-context and the familiarity-context group, data of one participant in the novelty-context group had to be discarded due to scanner failure) showed a higher activation for novel images in the novelty-context group than familiar images in the familiarity-context group in the left SN ($x = -12$, $y = -18$, $z = -10$), left posterior hippocampus ($x = -20$, $y = -32$, $z = -4$), and right posterior hippocampus ($x = 20$, $y = -32$, $z = 0$), left prefrontal cortex ($x = -44$, $y = 4$, $z = 26$), left insula ($x = -36$, $y = 18$, $z = -4$), and left anterior cingulate ($x = -2$, $y = 24$, $z = 46$) (Table 4).

To assess the relationship between free recall performance and brain activation during context exposure, we used free recall performance as a regressor in the SPM analysis contrasting novel images versus fixation and familiar images versus fixation across both groups. This revealed a correlation of free recall performance with activity in the bilateral prefrontal cortex [left Brodmann's area (BA) 6 and right BA 9], bilateral parahippocampal cortex (BA 36), and a region posterior to right SN (Figure 4A and B; Table 4). ROI analyses using activated voxels confirmed the correlations in the bilateral parahippocampal cortex [left $r(31) = .64$, $p < .01$; one-tailed; right $r(31) = .63$, $p < .01$; one-tailed] and left prefrontal cortex [$r(31) = .66$, $p < .01$; one-tailed] (Figure 4C and D). There was a significant positive correlation between left parahippocampal activation and free recall only for the novelty-context group [$r(15) = .80$, $p < .01$; one-tailed], but not the familiarity-context group [$r(16) = -.13$, $p = .32$; one-tailed] and we observed the same pattern in the left prefrontal cortex [novelty-context group: $r(15) = .78$, $p < .01$; one-tailed; familiarity-context group: $r(16) = -.08$, $p = .38$; one-tailed]. To further asses whether the two within-groups correlations differed, we applied a multiple regression using free recall performance, experimental group (novelty-context, familiarity-context), and the interaction of the two as predictor variables. A significant interaction of the two predictors would indicate a difference between the two within-group correlations. A significant interaction was found for the left parahippocampal ($p < .05$) and the left prefrontal cortices ($p < .05$).

Given our a priori hypotheses regarding the role of the SN/VTA in contextual memory enhancement, we extracted the contrast values (novel images versus fixation and familiar images versus fixation) of the significant local maximum in the SN/VTA and calculated its correlation with free recall. Figure 3D shows the novelty-related activation of this region (two-sample t test between the novelty- and the familiarity-context group) and the free recall performance for the two groups. The

Table 4. SPM Activations (Experiment 2)

		MNI Coordinates			
Region	*BA*	*x*	*y*	*z*	*z*
Two-sample t Test; p < .005, k = 100 voxels					
Right fusiform gyrus	37	26	−48	−10	5.63
Left cingulate gyrus	32	−2	24	46	5.12
Left posterior hippocampus		−20	−32	−4	5.12
Left SN/VTA		−12	−18	−10	3.97
Right posterior hippocampus		20	−32	0	3.90
Left insula	13	−36	18	−4	4.89
Right middle frontal gyrus	46	50	30	18	4.87
	6	32	−6	50	3.72
Left precentral gyrus	6	−44	4	26	4.73
Left fusiform gyrus	20	−32	−38	−18	4.63
Right claustrum		32	24	−2	4.66
Right cingulate gyrus	24	4	4	28	4.33
Left thalamus		−10	0	10	3.80
Regression of Free Recall Performance and Context Exploration; p < .005, k = 50 voxels					
Right midbrain		10	−26	−10	4.94
Right inferior frontal gyrus	9	40	8	22	4.52
Left precentral gyrus	6	−44	0	28	4.30
Right fusiform gyrus	37	40	−42	−10	4.09
Left parahippocampal gyrus	36	−22	−40	−12	3.98
Right parahippocampal gyrus	36	30	−40	−8	3.22

Significant activations found for SPM two-sample *t* test between the novelty- and familiarity-context groups and regression analysis of free recall performance and context exploration, collapsed over both context groups. BA refers to Brodmann's area. The coordinates are MNI coordinates provided by SPM2, the regions are reported in neurological convention.

overall correlation between the free recall performance and the contrast values in the left SN for all participants (i.e., for both groups) was significant [Figure 3D; $r(31) = .34$, $p = .03$; one-tailed, because both the direction of the correlation and its anatomical location were predicted]. However, there was no significant relationship within the novelty-context group alone [$r(15) = 0.14$, $p > .3$; one-tailed] and also not in the familiarity-context group [$r(16) = .09$, $p > .3$; one-tailed]. The multiple regression analysis also showed no difference between the two within-group correlations ($p > .9$), therefore, the relationship of memory performance and SN activation is consistent across the two groups. A similar analysis for two hippocampal regions that showed a novelty response also revealed neither a significant correlation with free recall performance [right hippocampal region: over both groups, $r(31) = .29$, $p > .5$, one-tailed; novelty-context group, $r(15) = -.16$, $p > .4$, one-tailed; and familiarity-context group, $r(16) = .13$, $p > .3$, one-tailed; left hippocampal region: over both groups, $r(31) = .05$, $p > .3$, one-tailed; novelty-context group, $r(16) = -.39$, $p > .05$, one-tailed; and familiarity-context group, $r(15) = -.41$, $p > .05$, one-tailed] nor were the within-group correlations different (right hippocampus: $p > .5$; left hippocampus: $p > .9$) (Figure 3E and F). However, compatible with recent models of a functional loop between the hippocampus and the SN/VTA (Lisman & Grace, 2005), hemodynamic responses in both regions were correlated [$r(31) = .53$, $p < .01$; one-tailed] while showing no correlations to parahippocampal responses (ps $> .05$; one-tailed) (Figure 6). Finally, the novelty responses in the insular cortex and the anterior cingulate (Table 4) did not show any correlation to memory enhancement (ps = .1 and .14, one-tailed) and the within-group correlations were also not different (ps $> .1$).

DISCUSSION

The results from Experiments 1 and 2 showed that a brief period of experiencing images of novel scenes reliably

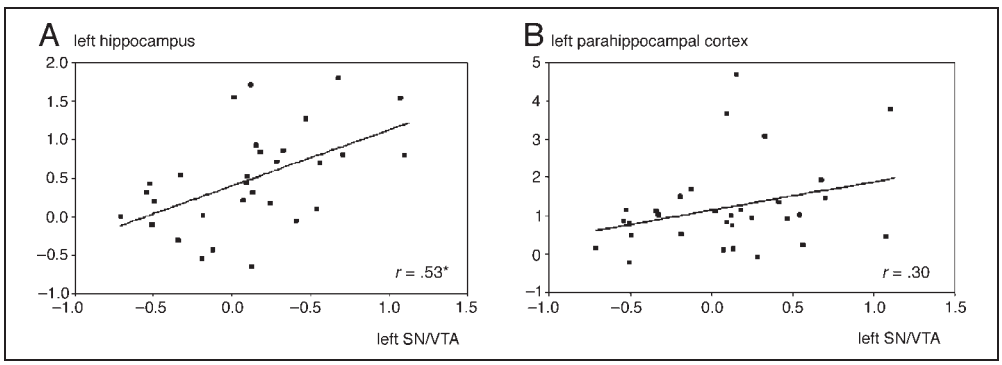

Figure 6. Scatterplot and correlation of left SN/VTA activation. The *x*-axes depict contrast values of images vs. fixation. (A) left SN/VTA activation and left hippocampal activation and (B) left SN/VTA activation and left parahippocampal activation (*y*-axes scale: contrast values of images vs. fixation). *r* refers to Pearson's correlation coefficient, the asterisks denote statistically significant correlations.

enhanced subsequent memory formation in humans. A selective effect on recollection as observed in Experiment 1 is compatible with a hippocampus-dependent effect, given that relatively selective hippocampal damage can have mild effects on overall recognition memory scores (Yonelinas et al., 2002; Vargha-Khadem et al., 1997) and behavioral consequences of such injury become most marked in ANOVAs contrasting the proportions of recollection and familiarity estimates (Yonelinas et al., 2002), as done in the present study. The enhancement in Experiment 2 was shown using free recall, a measure that is held to rely on recollection only (Yonelinas et al., 2002), is more strongly affected by relatively selective hippocampal injury (Yonelinas et al., 2002; Vargha-Khadem et al., 1997) than overall recognition memory, and is associated with hippocampal activation at the time of encoding (Schott et al., 2006). Both experiments thus provide converging support that novel context enhanced hippocampus-dependent memory formation. Furthermore, both experiments show a clear effect on encoding, indicating that contextual enhancement of memory by novelty is not selective to improving consolidation. However, Experiment 1 additionally suggests an effect on the consolidation of words studied prior to a novel context (Figure 5B).

Animal studies suggest that the contextual enhancement of hippocampal plasticity by novelty can be observed within around 30 min after context exposure (Li et al., 2003; Straube et al., 2003). Although the free recall part of Experiment 2 was comfortably within this time window (approximately 15–25 min after novelty exposure), the study phase of recognition memory was partly outside (approximately 25–40 min). Although this might have been one reason why there was no selective enhancement of recollection following the significant enhancement of free recall [but note that we did observe a trend for nonselective improvement of overall recognition memory in the novelty context of Experiment 2; $F(1, 29) = 3.48$, $p = .07$], determining the temporal extent of memory enhancement after exposure to novelty would require a parametric manipulation of the delay between context exposure and study phase. Other factors that might have contributed to weakening the effects of novelty context on the recognition memory part of Experiment 2 are interference from the preceding free recall and exposure to the familiarity of the words used in the free recall task. Finally, unlike the free recall experiment, participants were faster in the study phase of the recognition memory experiment in the novelty context in contrast to familiarity context (Table 3), suggesting that the trend for better recognition memory was, in part, perhaps also due to higher arousal (or less fatigue) in the second encoding session of the novelty-context group. All this said, our findings show improvement of hippocampus-dependent memory performance with two different memory measures, recollection and recall, providing converging evidence that a brief exposure to novel context enhances hippocampus-dependent memory.

The enhancement of recollection and recall following the novelty context together with a higher hemodynamic response in the SN/VTA elicited by novel as compared to familiar images (evident in the group contrasts of the functional data from Experiment 2) highlights a remarkable parallel between findings regarding dopaminergic enhancement of hippocampal plasticity in the context of novelty in rodent studies (Li et al., 2003; Straube et al., 2003) and contextual modulation of memory in humans. Also, the amount of activation of the SN/VTA region that displayed this novelty response was positively correlated with free recall performance across both groups (Figure 3D). However, contrary to our expectation, the amount of novelty-related SN/VTA activation within the novelty group was not correlated with free recall performance. Other areas implicated in novelty processing in many previous studies (Hasselmo & Stern, 2006; Nyberg, 2005; Duzel, Habib, Guderian, & Heinze, 2004; Yamaguchi, Hale, D'Esposito, & Knight, 2004; Duzel et al., 2003; Ranganath & Rainer, 2003; Tulving, Markowitsch, Kapur, Habib, & Houle, 1994), including the hippocampus bilaterally (Figure 3C), the insular and prefrontal cortices bilaterally, and the right cingulate gyrus (Table 4), were also more active in the group contrasts between the novelty context and the familiarity context. Of these regions, activations in parahippocampal and dorsal prefrontal cortices during novelty exposure strongly correlated with free recall performance in the novelty group (Figure 4A and B). In the face of these strong correlations, our findings regarding the SN/VTA suggest that its activation might have little quantitative relationship to contextual memory enhancement. Compatible with recent models of a functional loop between the hippocampus and the SN/VTA (Lisman & Grace, 2005), hemodynamic responses in both regions were correlated while showing no correlations to parahippocampal responses (Figure 6). Along these lines, we have previously reported that single exposures to familiar stimuli are sufficient to elicit a response decrement in the SN/VTA, which parallels remarkably well response decrements in the hippocampus (Bunzeck & Duzel, 2006). These parallels between novelty responses in the hippocampus and the SN/VTA make it unlikely that the SN/VTA response to novelty was, in some way, atypical, and therefore, the lack of a quantitative relationship with memory enhancement was a regionally specific methodological artifact. Rather, there may be physiological reasons why the relationship between SN/VTA (and hippocampus) responses to novelty and contextual memory enhancement may be qualitative rather than qualitative that future studies may help to uncover.

Our data emphasize the quantitative role of scene processing and attentional orienting to novel stimuli in contextual memory enhancement. The dorsal superior prefrontal cortical region (BA 6) is part of the lesion

sites that have been reported (Daffner et al., 2000) to be associated with a deficit in directing attention toward novel events. Its activation pattern shows a combination of sensitivity to novelty as well as a strong correlation with memory enhancement, making it plausible that its activation is related to the amount of attention that subjects directed toward the novelty of stimuli. The location of the correlations between memory enhancement and parahippocampal activity is well compatible with the parahippocampal place area implicated in the processing of images of scenes (Tong et al., 1998).

Both experiments were designed to minimize possible differences in vigilance and arousal between novelty- and familiarity-context groups by presenting all participants with a series of familiar images prior to word list learning. RT data during word list learning show no differences (at study) as a function of context in Experiment 1 and the free recall part of Experiment 2, making strong group differences in vigilance and arousal levels unlikely. This is also weakened by the lack of memory enhancement after the emotional context in Experiment 1. Furthermore, although the novelty responses in the insular cortex and the anterior cingulate (Table 4) in Experiment 2 could be interpreted as arousal- or vigilance-related (Critchley, 2005), their activity (extracted from the peak difference between the novelty- and the familiarity-context group), unlike the left SN/VTA novelty response, did not show any correlation to memory enhancement. We therefore think that the memory enhancement after novelty context was not simply due to vigilance or arousal.

If effects of novelty context extend over a time period of around 30 min after exposure to novelty (Li et al., 2003; Straube et al., 2003), then in order to detect the effects of novelty on hippocampus-dependent memory, the separation of experimental blocks with and without novel stimuli should be at least 30 min. In a recent behavioral study (Bunzeck & Duzel, 2006), we observed an enhancement of learning by novelty, when the novel context and familiar context were separated by only 6 min. As expected, this enhancement was not selective to recollection and was more short-lasting than in Experiment 1 of the present study. This suggests that novelty might perhaps exert two different forms of contextual enhancement, one that is long-lasting and relatively specific to recollection and can be observed within 30 min after exposure to novelty, and a second that is shorter-lasting and less selective to recollection and can be observed within minutes after exposure to novelty. Cognitive models of novelty processing on memory stress the immediate effects of novelty on attention and memory for the novel stimulus itself (e.g., Mesulam, 1998; Tulving & Kroll, 1995; Tulving et al., 1994; von Restorff, 1933). The present findings of long-lasting neuromodulatory effect of novelty on the encoding of unrelated stimuli has yet to be incorporated into cognitive models of human novelty processing and memory in the human brain.

Taken together with our previous findings (Bunzeck & Duzel, 2006), the present data suggest that a combination of a prelearning exposure to novelty, in addition to intermittent presentation of novel stimuli during learning, might provide the strongest enhancement of learning, boosting overall recognition memory in addition to boosting recollection. The implications of the present findings also extend to the relationship between learning and consumption of media such as television and computer games. They suggest that repeated exposure to arousing material, such as time spent on a familiar computer game, should have no beneficial effect on learning. Viewing novel images from the National Geographic, on the other hand, should boost learning. The novel images of scenes in the current experiments were selected randomly and were unrelated to the words used to probe memory enhancement. Hence, memory enhancement by the neuromodulatory, attentional, and exploratory components of novelty appear to extend beyond categories and it would be interesting to determine whether they also extend across modalities such as from visual novelty to auditory learning. Finally, although we did not observe a clear quantitative relationship between SN/VTA activation and contextual memory enhancement, this does not rule out the possibility that dopaminergic neuromodulation plays a critical role here. It is possible that pharmacological studies could identify a critical role in contextual enhancement for both dopaminergic and noradrenergic neuromodulation using the cognitive principles uncovered here.

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