

Negative Emotional Experiences during Navigation Enhance Parahippocampal Activity during Recall of Place Information

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Abstract

■ It is known that the parahippocampal cortex is involved in object–place associations in spatial learning, but it remains unknown whether activity within this region is modulated by affective signals during navigation. Here we used fMRI to measure the neural consequences of emotional experiences on place memory during navigation. A day before scanning, participants undertook an active object location memory task within a virtual house in which each room was associated with a different schedule of task-irrelevant emotional events. The events varied in valence (positive, negative, or neutral) and in

their rate of occurrence (intermittent vs. constant). On a subsequent day, we measured neural activity while participants were shown static images of the previously learned virtual environment, now in the absence of any affective stimuli. Our results showed that parahippocampal activity was significantly enhanced bilaterally when participants viewed images of a room in which they had previously encountered negatively arousing events. We conclude that such automatic enhancement of place representations by aversive emotional events serves as an important adaptive mechanism for avoiding future threats. ■

INTRODUCTION

Successful navigation requires accurate encoding and retrieval of spatial information. To date, however, the possible influence of emotional events on spatial learning during navigation has not been investigated. Several studies have suggested that emotional arousal can exert a powerful influence on memory, enhancing recall under some conditions and disrupting it under others (Reisberg & Heuer, 2004; Buchanan & Adolphs, 2002). In extreme cases, traumatic emotional events can even cause hypermnesia, a prominent symptom of posttraumatic stress disorder (PTSD; Brohawn, Offringa, Pfaff, Hughes, & Shin, 2010; Wessa, Jatzko, & Flor, 2006). Under different circumstances, however, threat-induced enhancement of memory representations might constitute an important survival mechanism (e.g., Hamann, 2001). Successful learning of the location at which a negative event was previously encountered might provide an important cue for avoiding threats in the future.

Extensive research has attributed the encoding and recall of place and scene information during navigation to the parahippocampal cortex (Baumann, Chan, & Mattingley, 2010; Epstein, 2008; Maguire, Frith, Burgess, Donnett, & O’Keefe, 1998). Moreover, recent studies have suggested that the parahippocampal cortex automatically

codes for the navigational relevance of objects in the environment (e.g., Janzen, Wagensveld, & van Turenout, 2007; Janzen & van Turenout, 2004). Activity in the parahippocampal gyrus is enhanced for objects previously placed at important navigational decision points (e.g., at T-intersections) compared with objects placed at navigational non-decision points (e.g., at L-junctions). As yet, however, it remains unclear whether activity within the parahippocampal cortex is also regulated by the emotional salience of specific locations encountered during navigation.

Previous findings suggest that arousing events might play a direct role in memory enhancement, most likely via activation of the amygdala, a region crucial for emotional processing (Hamann, Ely, Grafton, & Kilts, 1999; LeDoux, 1992a). Activity in the amygdala can enhance postencoding consolidation processes in medial-temporal regions such as the hippocampus and parahippocampal gyrus (Kilpatrick & Cahill, 2003). Once enhanced, these affectively tagged traces are stored in long-term memory for later access, independent of the amygdala circuitry that contributed to their creation (Cahill & McGaugh, 1998). Beyond the spatial domain, parahippocampal cortex has also been found to be important in the encoding of emotionally salient information, particularly for negative emotions (Murty, Ritchey, Adcock, & LaBar, 2010; Gosselin et al., 2006).

Here we used fMRI to examine the influence of emotional experiences on place memory formed during active

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navigation through a virtual environment (Figure 1). The experiment consisted of two phases: a “learning phase,” in which participants actively navigated through rooms of a virtual house, and a subsequent “retrieval phase,” conducted 1 day later, in which participants were shown static scenes from the house while being scanned (Figure 2). During the learning phase, each room was associated with a different schedule of task-irrelevant emotional stimuli, which varied both in their valence (positive, negative, or neutral) and in their rate of occurrence (intermittent vs. constant). During the retrieval phase a day later, participants viewed static images taken from within the rooms and completed an object location retrieval task. Critically,

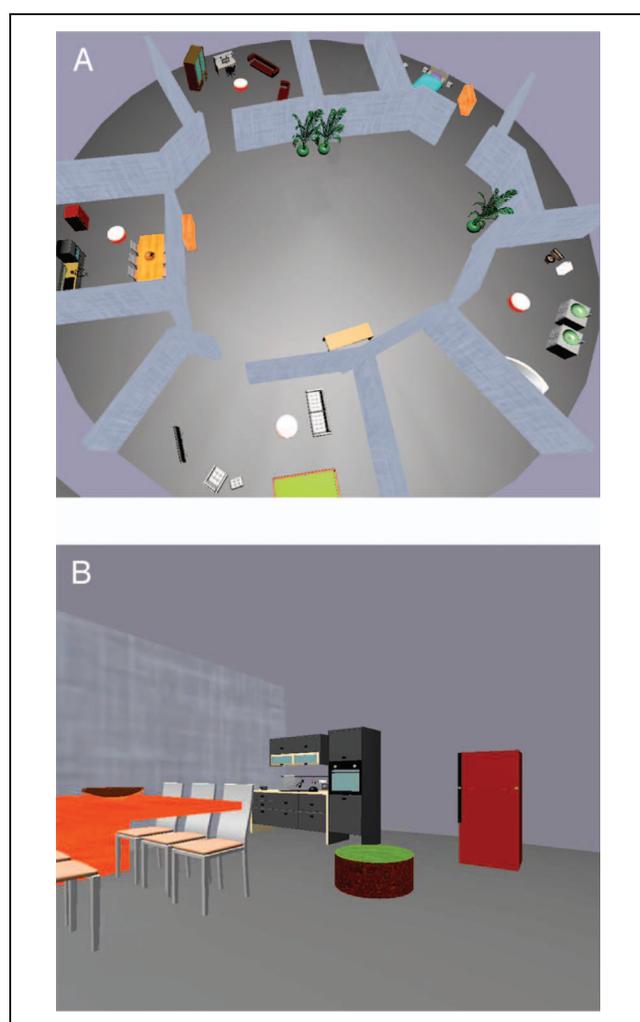


Figure 1. Schematic of the virtual arena used in the experiment. (A) Aerial perspective of the virtual arena containing the five distinct rooms. Participants began each learning trial from the center of the arena and navigated to the different rooms via openings in the inner wall. (B) Example of a view experienced by participants when they entered a room during the learning phase. Participants discovered the correct location for each target item (a simple line drawing of a familiar object) by approaching the cylindrical container (“bin”) in each room and making a button press to query the location as being correct or incorrect.

no emotion-evoking stimuli were shown during this retrieval phase, and participants were not required to recall the emotional events while completing the task. We predicted that negative emotional events encountered during navigation would enhance neural activity triggered by images of rooms with which those events were associated and that this enhancement would be most prominent within the parahippocampal cortex, consistent with its role in coding the spatial relevance of place information (Janzen & van Turennout, 2004).

METHODS

Participants

Twenty healthy, adult volunteers (10 women) gave their informed consent to participate in the study, which was approved by the Human Research Ethics Committee of The University of Queensland. Their mean age was 24 years (range = 18–35 years). All participants were right-handed and had normal or corrected-to-normal vision.

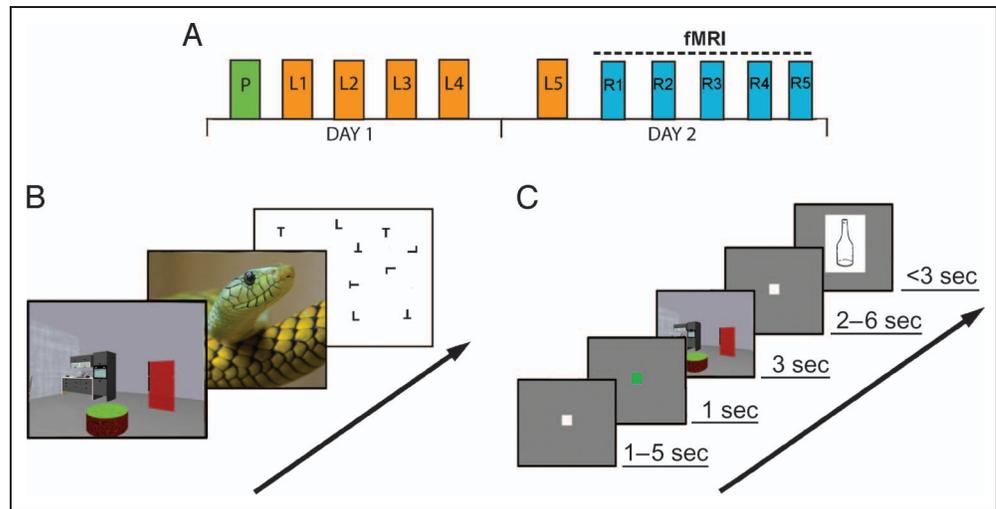
Design and Procedure

Learning Phase

Participants navigated within a virtual house (radius = 23 m) containing five distinct rooms (see Figure 1). The virtual environment was created using the Blender open source 3-D content creation suite (The Blender Foundation, Amsterdam, Netherlands) and presented on a 21.5-in. LCD monitor. Participants navigated the environment from a first-person perspective using a handheld joystick. Each of the five rooms within the virtual environment was randomly allocated to one of the five critical conditions, with the factors of valence (positive, negative) and rate of occurrence (intermittent, constant) being crossed to yield four of the conditions. In the intermittent schedules, emotionally arousing events occurred on 50% of the trials, and neutral (nonarousing) events were randomly intermingled on the other 50% trials. In the remaining room, only neutral (nonarousing) events were presented to act as a baseline. Our aim with this manipulation was to test whether any effects on place memory and associated neural responses are modulated by the relative surprise of the emotion-inducing events (den Ouden, Friston, Daw, McIntosh, & Stephan, 2009; Bermpohl et al., 2006; Strange, Duggins, Penny, Dolan, & Friston, 2005).

Emotions were elicited using photographs of scenes drawn from the International Affective Picture System (IAPS) library (Lang, Bradley, & Cuthbert, 1999), a set of color photographs that includes affective ratings on a 9-point scale, along the two dimensions of valence (ranging from 1 = *very unpleasant* to 9 = *very pleasant*) and arousal (ranging from 1 = *least arousing* to 9 = *most arousing*) made by men and women (Lang et al., 1999). The IAPS ratings are based on the assumption that

Figure 2. Overview of experimental design and sequence of trial events. (A) The experiment was conducted over two consecutive days. Task practice (P) and learning (L) were completed on Day 1, and the retrieval phase (R) was completed on Day 2 while undergoing fMRI. (B) Each learning trial consisted of three distinct and nonoverlapping components: an active object location navigation task, an emotional event (IAPS picture: positive, negative, or neutral), and a visual search buffer task. (C) During the retrieval phase, participants were shown a static image taken from within one of the five rooms, followed by a target object. Participants had to indicate via button press whether the object belonged in the room depicted in the preceding snapshot.



two motivational systems exist in the brain—appetitive and aversive/defensive—that account for the primacy of the hedonic valence and arousal dimensions in emotional expression (Lang, 1995; Lang, Bradley, & Cuthbert, 1990). According to this view, the diversity of all expressed emotions (e.g., fear, anger, happiness) can be attributed to activation in these two basic motivational systems. The IAPS provides a standardized approach to evoking and assessing emotions in a controlled manner and has been extensively tested for reliability and validity (Bradley & Lang, 2007). The 120 images (neutral = 48, positive = 36, negative = 36) were selected based on the IAPS normative ratings, in line with several earlier neuroimaging studies (e.g., Baucom, Wedell, Wang, Blitzer, & Shinkareva, 2012; Baumann & Mattingley, 2012; Crawford & Cacioppo, 2002; Keil et al., 2002). The neutral images were chosen to be low in arousal (mean = 2.66; $SD = 0.38$) and intermediate in valence (mean = 4.91, $SD = 0.05$), whereas positive and negative images were chosen to be equally high in arousal (positive: mean = 5.98, $SD = 0.85$; negative: mean = 6.28, $SD = 0.73$) and opposite in valence (positive: mean = 7.20, $SD = 0.66$; negative: mean = 2.18, $SD = 0.45$). The level of arousal was therefore matched between positive and negative images. Pleasant pictures included couples, happy families, scenes of sports and adventure; unpleasant pictures included mutilated bodies and scenes of attack and threat; neutral pictures included neutral-faced men and women as well as household items. Each IAPS image was presented only once throughout the learning phase, so that each room was

pseudorandomly associated with several different images from various picture categories.

During the learning phase, participants completed a 20-item object location learning task. On each trial, participants were transported to the center of the virtual house facing one of four directions. One of 20 images depicting line drawings of familiar objects was displayed in the corner of the computer screen, and participants were told that they had to discover and remember the room in which the object belonged as they navigated freely through the environment. Each of the five rooms was pseudorandomly assigned to 4 of the 20 objects. Participants were explicitly told that this was their main task, and their knowledge of object locations would be tested the following day. Object stimuli were familiar, neutral items (e.g., cup, bottle), preselected from the Snodgrass and Vanderwart object database (Snodgrass & Vanderwart, 1980). When participants entered a room within the virtual environment, they were instructed to approach the cylindrical container (“bin”) and to press a button on the joystick to query whether the target object belonged in that room. The appearance of a red cross above the container indicated that the object did not belong in that room, in which case participants were to continue searching for the correct object location by navigating to another room. Correct placement of an object resulted in the disappearance of the object picture and the termination of the trial. After a brief delay (1 sec) in which the screen remained blank, an IAPS image was presented for 3 sec (Figure 2B). The valence of the IAPS image shown corresponded to the schedule of emotional events assigned

to the particular room. For the rooms assigned with an intermittent schedule, the presentation of positive or negative versus neutral images was randomized between trials, and these images were unrelated to the object being placed on any given trial. Critically, neutral, positive, and negative images were not shown within the rooms, as the aim was to minimize any explicit association between the IAPS pictures and the locations being explored. We also wished to avoid any interference that might be caused by the IAPS images while participants were learning the associations between objects and rooms. Participants were told to pay attention to the IAPS pictures, but it was made explicit that the pictures were unrelated to the critical object location learning task and thus that they were not required to remember them.

To minimize the possibility that the emotional response elicited by the IAPS images might carry over to the next learning trial, participants were required to undertake a difficult visual search task, which acted as an affective “buffer” at the end of every trial (Figure 2B; Schwarze, Bingel, & Sommer, 2012). The visual search task required participants to search for a target letter (a leftward or rightward rotated T) among distractors (40 upright and inverted Ls and Ts). Participants indicated the direction of the target letter rotation using a two-alternative button-press response. There was no time limit on the task, and participants were told only to respond when they had found the target letter.

In total, participants completed five learning blocks (Figure 2A). Four blocks were completed in succession within one session, and an additional block was completed before the retrieval phase on the following day. Within each block, each target object was presented once in a pseudorandomized order. Before the first learning block, a practice block was given in which an arrow appeared above the cylindrical container (“bin”) at the correct location for each trial to assist participants in learning the object location associations.

Retrieval Phase

We measured neural responses with fMRI while participants completed a yes/no object location decision task based on the associations they formed during the learning phase (Figure 2C). Participants viewed pairs of static images of locations and objects, presented successively, and responded as quickly and as accurately as possible to indicate whether the target object (1 of the 20 used during the learning phase) belonged in the depicted room (match trials) or did not belong there (nonmatch trials). Responses were made using the right hand via a two-alternative button box (yes/no). During the retrieval phase, participants were not required to navigate, and no emotional stimuli were presented. Thus, while in the scanner, participants only viewed static images of room locations and objects that could belong within them, as shown in Figure 2C.

Each test trial consisted of a fixation point (white dot; 1–5 sec) and a cue (green dot; 1 sec), followed by a static snapshot taken from within one of the five rooms (3 sec). Participants were asked to visualize the room shown, but no overt response was required. After a delay period (white dot; 2–6 sec), the room snapshot was replaced by a target object (1 of the 20 objects used during the learning phase), which remained visible for a maximum of 3 sec or until a response was made by the participant. Participants completed five blocks of test trials. Each block consisted of 40 trials (20 match, 20 nonmatch), with each target object appearing twice (one match trial, one nonmatch trial). Four different snapshot views taken from within each virtual room were presented during the retrieval phase. Each snapshot was chosen to be maximally distinct from the other three taken within the same room, by encompassing different combinations of furniture, walls, and other items. Trials were delivered using Presentation software (Neurobehavioral Systems; www.neurobs.com). Responses and RT data were recorded for off-line analysis. The sequencing of the trials, as well as the temporal jittering of rest periods, was optimized with optseq2 software (surfer.nmr.mgh.harvard.edu/optseq/). At the conclusion of the experiment, all participants completed a questionnaire asking them to describe any associations they had noticed between the different rooms of the virtual house and the types of emotional images shown at those locations during the learning phase of the task.

fMRI Methods

Whole-brain EPI was conducted on a 3T MR scanner (Trio; Siemens, Erlangen, Germany) with a 32-channel head coil. Thirty-six axial slices (slice thickness, 3.3 mm) were acquired in an interleaved order, using a gradient-echo echo-planar T2*-sensitive sequence (repetition time = 2.41 sec, echo time = 30 msec, flip angle = 90°, matrix = 64 × 64, field of view = 210 × 210 mm, voxel size [spacing] = 3.3 × 3.3 × 3.3 mm). A T1-weighted structural MP-RAGE was also acquired. A liquid crystal display projector (1024 × 768 resolution) back-projected the retrieval phase trials onto a screen positioned at the head of the scanner gantry. Participants lay on their backs within the bore of the magnet and comfortably viewed the stimuli via a 45°-angled mirror that reflected the images displayed on the screen. The distance to the screen was 90 cm (12 cm from eyes to mirror), and the visible part of the screen encompassed approximately 22.0° × 16.4° of visual angle (35.5 × 26 cm). All participants were stabilized with tightly packed foam padding surrounding the head to minimize head movement.

Image processing and statistical analyses were performed using SPM5 (Wellcome Department of Imaging Neuroscience, UCL, London, UK). Functional data volumes were slice-time corrected and realigned to the first volume. A T2*-weighted mean image of the unsmoothed images was coregistered with the corresponding anatomical

T1-weighted image from the same individual. The individual T1 image was used to derive the transformation parameters for the stereotaxic space using the SPM5 template (Montreal Neurological Institute [MNI] Template), which was then applied to the individual coregistered EPI images. The voxel sizes of the normalized images were 2 mm^3 . Images were then smoothed with an 8-mm FWHM isotropic Gaussian kernel. As we were interested in the influence of the schedule of emotional events during learning on subsequent place memory, the location screens for the five different rooms were modeled separately as boxcar functions convolved with a hemodynamic response function; the target object screen was modeled separately as a regressor of no interest, pooled over the five rooms. We increased the sensitivity of our analysis by focusing on selected brain regions that we hypothesized should be involved in place memory processes. We undertook a small volume corrected analysis targeting the parahippocampal gyrus, separately within the left and right hemisphere. We also conducted a targeted analysis of activity in the hippocampus and amygdala, given their established roles in spatial (Burgess, Maguire, & O'Keefe, 2002; Maguire, Burgess, & O'Keefe, 1999) and emotional processing (LeDoux, 1992b), respectively. ROIs were defined using the AAL atlas (Tzourio-Mazoyer et al., 2002) and WFU pickatlas tool (Maldjian, Laurienti, Kraft, & Burdette, 2003).

Our principal comparison during the retrieval phase involved testing for differences in neural activity between the consistently negative and positive locations and the neutral location (as a nonarousing baseline). We also tested for differences between the intermittent emotional schedules and the neutral condition. Statistical parametric maps of the t statistic were generated for each participant from linear contrasts for the condition of *Consistent negative* > *Neutral* and *Consistent positive* > *Neutral*, as well as *Intermittent negative* > *Neutral* and *Intermittent positive* > *Neutral*. These contrasts of parameter estimates were then included in a second-level group analysis using single-sample t tests on the contrast images obtained from each participant.

In addition, we conducted a secondary analysis to examine potential interactions between the valence of the emotional events and their rate of occurrence. We used the MarsBaR toolbox (marsbar.sourceforge.net/) to extract and calculate the average BOLD signal change for the left and right parahippocampal gyrus (according to the AAL atlas; Tzourio-Mazoyer et al., 2002), separately for all participants, for each emotional event type. Extracted percentage signal change values for the two regions were submitted to separate two-way ANOVAs with factors of Valence (positive, negative) and Rate of Occurrence (constant, intermittent).

RESULTS

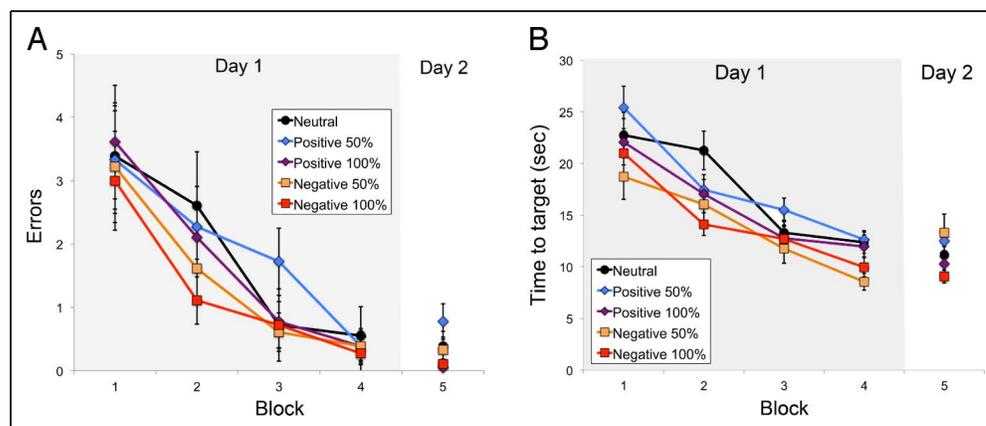
Behavioral Performance

Learning Phase

As expected, memory for object locations improved with learning in the prescan sessions (Figure 3A). Across the five learning blocks, there was a steady decline in the number of times participants navigated to an incorrect room. Consequently, trial duration (i.e., the time required by participants to navigate to the correct room) also decreased across learning blocks, from an average of 22.01 sec ($SD = 9.49$) in the first block to 11.28 sec ($SD = 4.86$) in the fifth block (see Figure 3B). An ANOVA on error rates, with factors of Learning (Blocks 1–5) and Emotional Event Schedule (100% positive, 100% negative, 50% positive, 50% negative, and neutral) revealed a significant main effect of Learning, $F(4, 76) = 21.937, p < .01$. There was no main effect or interaction involving the factor of Emotional Event Schedule. An ANOVA on trial duration, with factors of Learning (Blocks 1–5) and Emotional Event Schedule (100% positive, 100% negative, 50% positive, 50% negative, and neutral) revealed a significant main effect of Learning, $F(4, 76) = 48.008, p < .01$; a significant main effect of Emotion, $F(4, 76) = 4.065, p < .01$; and a significant interaction between Learning and Emotion, $F(16, 304) = 2.663, p < .01$. Inspection of the pattern of learning across blocks (see Figure 3B) suggests

Figure 3. Behavioral results from the learning phase.

(A) Mean error rate in the object location task across the five learning blocks, expressed as the average number of incorrect locations queried on each trial. (B) Mean exploration time (sec) in the object location task across the five learning blocks.



that participants completed trials more quickly for all five emotional event schedules, but at slightly different rates between Block 1 and Block 5. Some caution is required in interpreting these results, however, as our instructions to participants emphasized accuracy rather than speed.

Taken together, the behavioral data indicate that participants learned the object–room associations over the course of the five prescan blocks, reducing both their error rates and the time required to reach the appropriate room. Although the time-to-target data suggest differences in the rate of learning across the five emotional event schedules, these did not follow a consistent pattern. Interestingly, results from a postexperimental questionnaire revealed that no participant was explicitly aware of any consistent association between particular rooms and the emotional events with which they were paired.

Retrieval Phase

Overall accuracy on the object location task during fMRI scanning was 93%. Only correct trials were included in the analyses of RT data (Figure 4); the relatively small number of incorrect trials did not permit assessment of potential interactions between performance on nonmatch trials and emotional events.

Effect of Emotional Events Compared with Neutral Baseline

Planned pairwise comparisons revealed that, relative to RTs to stimuli associated with the neutral location ($M = 0.99$ sec [0.15]), participants responded significantly faster for object locations at which there was a constant

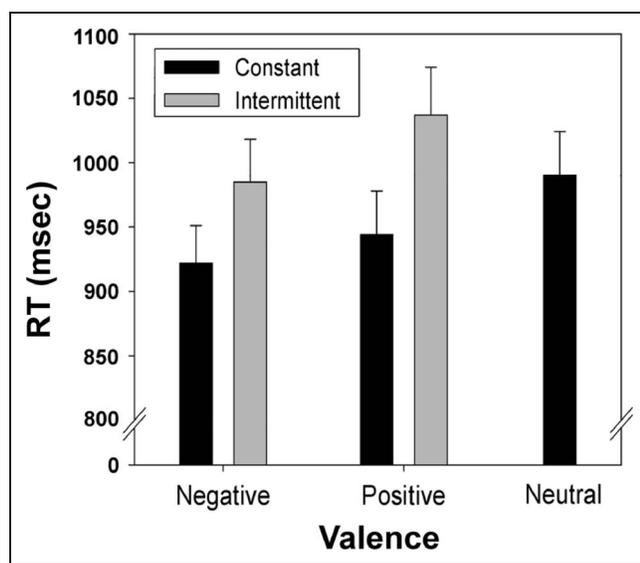


Figure 4. Effects of emotion on retrieval speed. Mean RT (msec) for the object location task in the retrieval phase for each of the five event schedules (one of which was associated with each of the five different rooms).

negative event schedule ($M = 0.92$ sec [0.13], $t(19) = -5.12$, $p < .01$) or a constant positive event schedule ($M = 0.94$ sec [0.15], $t(19) = -3.15$, $p < .01$).

Effect of Different Emotional Event Schedules

Results revealed that the different emotional event schedules during learning had an influence on subsequent retrieval. A two-way ANOVA, with factors of Valence (positive, negative) and Event Schedule (intermittent: 50% emotional events, constant: 100% emotional events) revealed that responses to identify object locations were significantly faster for rooms associated with a constant schedule of emotional events than for rooms associated with an intermittent schedule, irrespective of valence, $F(1, 19) = 32.46$, $p < .01$. In addition, responses were significantly faster for locations associated with negative events than for locations associated with positive events, $F(1, 19) = 7.78$, $p < .05$ (Figure 4). There was no significant interaction between Valence and the type of Event Schedule. It is important to note that RTs were determined from the onset of the object display and that room snapshots appeared 5–9 sec beforehand (see Figure 2). Participants could therefore begin retrieving information about object identity several seconds before an object image actually appeared. It is possible, therefore, that the RTs reported here potentially underestimate the actual time it took participants to retrieve objects from memory. Nevertheless, any such effect would have applied equally to all emotion schedules and so should not have systematically biased the observed differences between the conditions (i.e., reliably faster responses for constant negative and positive emotional schedules than for intermittent schedules or the neutral baseline).

Overall, the results of the retrieval phase revealed that emotional events encountered incidentally during navigation enhanced retrieval speed for object location associations. Our results are consistent with previous studies that have shown enhanced retrieval performance for information paired with arousing stimuli during encoding and consolidation (Davis et al., 2011; Knight & Mather, 2009; Anderson, Wais, & Gabrieli, 2006; Nielson, Yee, & Erickson, 2005). The finding that retrieval speed was significantly faster for negative compared with positive locations supports the view that emotional enhancement effects are valence specific.

fMRI Results

A small volume corrected analysis targeting the left and right parahippocampal gyrus was conducted, comparing activity elicited by locations associated with consistently negative and positive events, with activity elicited by the location associated with neutral events only (corrected for multiple comparisons, $p < .05$, FWE). These comparisons revealed significantly greater activity in the left ($t = 7.83$, cluster size of 104, MNI coordinates of the peak

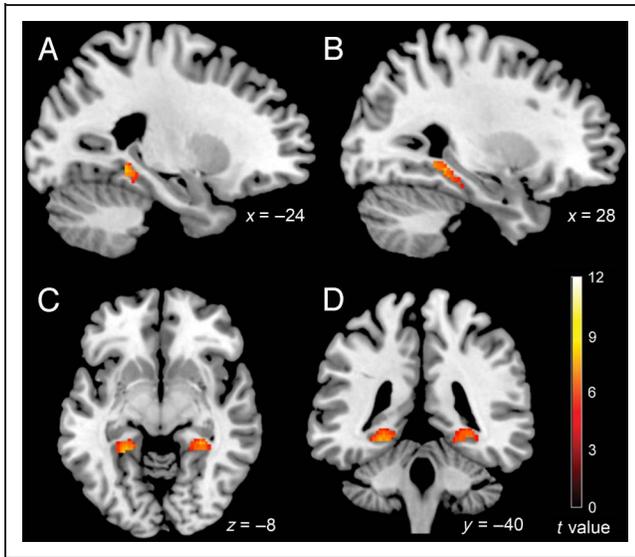


Figure 5. Neural activity within the parahippocampal gyrus during the retrieval phase. Mean BOLD activity for the comparison of the consistent negative > neutral location, showing increased activity in the left and right parahippocampal regions (small volume corrected threshold $p < .05$, FWE, corrected for multiple comparisons). Activations are displayed on (A) left and (B) right sagittal slices, (C) an axial slice, and (D) a coronal slice from an MNI-normalized template brain.

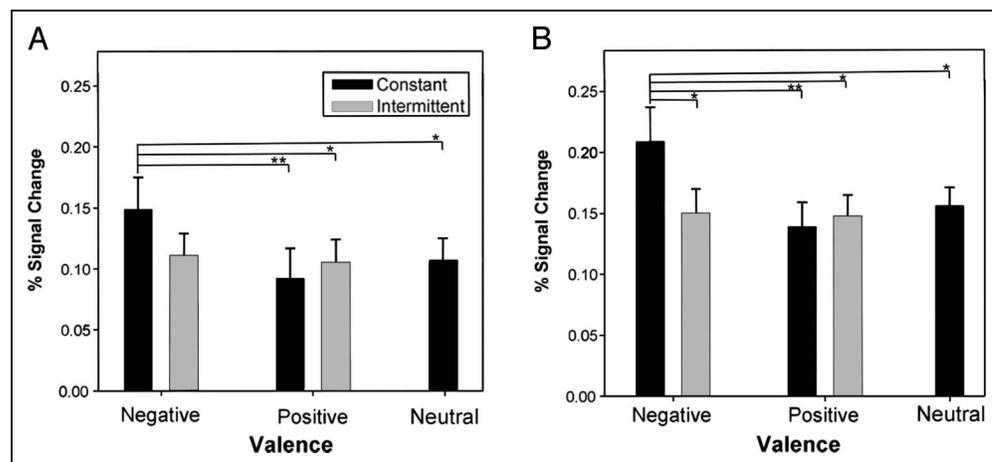
voxel: $-24, -42, -8$) and right ($t = 7.75$, cluster size of 156, MNI coordinates of the peak voxel: $28, -38, -8$) parahippocampal gyrus during exposure to locations that had consistently been associated with negative affective stimuli (see Figure 5). By contrast, there was no significant difference in activity for comparisons involving locations consistently associated with positive affective stimuli. Moreover, a comparison between locations associated with intermittent emotional events (both positive and negative) compared with locations associated with neutral events only did not yield any significant results. We also examined the possible involvement of the amygdala and

hippocampus during object location retrieval, given the established role of these structures in emotion processing (LeDoux, 1992b) and spatial memory (Burgess et al., 2002; Maguire et al., 1999), respectively. Using a small volume corrected analysis approach, we compared activity elicited by locations associated with consistently negative and positive events, with the neutral baseline. No significant differences in activity were revealed by these comparisons, suggesting that any contribution of signals from amygdala and hippocampus during the initial learning phase was no longer required at retrieval.

Whole-brain level analyses (corrected for multiple comparisons, $p < .05$, FWE) further confirmed these findings. A comparison of locations associated with consistently negative events and the location associated with neutral events revealed only two significant clusters of activity corresponding to the left ($t = 8.09$, cluster size of 19, MNI coordinates of the peak voxel: $-26, -46, -6$) and right ($t = 7.83$, cluster size of 6, MNI coordinates of the peak voxel: $28, -46, -6$) parahippocampal gyrus. These two activation clusters are in proximity to the parahippocampal place area (Epstein, Harris, Stanley, & Kanwisher, 1999). By contrast, there were no significantly activated voxels for comparisons involving locations consistently associated with positive affective stimuli or for locations associated with intermittent emotional event schedules (both positive and negative).

In a secondary analysis, we examined potential interactions between the valence of the emotional events and their rate of occurrence on neural activity within the parahippocampal gyri. Average percentage signal change was extracted using MarsBar (marsbar.sourceforge.net/) for the left and right parahippocampal gyrus (according to the AAL atlas; Tzourio-Mazoyer et al., 2002), separately for all participants, for each emotional event type (see Figure 6). These activation data were subjected to a two-way ANOVA, with factors of Valence (positive, negative) and Rate of Occurrence (constant, intermittent). Results revealed a significant main effect of Valence for

Figure 6. Percentage BOLD signal change within the parahippocampal gyrus during the retrieval phase. (A, B) Regionally averaged percentage BOLD signal change for the left and right (A and B, respectively) parahippocampal gyrus (anatomical definition according to the AAL atlas; Tzourio-Mazoyer et al., 2002), shown separately for the five affective event schedules. The black brackets indicate statistically significant differences between the different affective event schedules (paired t tests, $*p \leq .05$; $**p \leq .001$).



both the left and right parahippocampal gyri (left, $F(1, 19) = 6.94, p < .05$; right, $F(1, 19) = 5.28, p < .05$). This main effect was modified by a significant interaction between Valence and Rate of Occurrence (left, $F(1, 19) = 5.18, p < .05$; right, $F(1, 19) = 8.47, p < .05$; Figure 6). This interaction was driven by enhanced activity within the parahippocampal gyri when participants viewed a location that had consistently been associated with negative affective stimuli during learning, compared with the other affective event schedules. Paired t tests revealed that the difference between the consistent negative and consistent positive affective event schedules was statistically highly significant ($p = .001$), for both the left and the right parahippocampal gyrus (see Figure 6).

DISCUSSION

We used fMRI to investigate whether incidental encounters with affective stimuli during navigation affect neural activity during subsequent retrieval of place information. In line with our hypothesis, we found that memory-related parahippocampal activity was modulated by the emotional salience associated with places visited in a virtual environment on the day before scanning. More specifically, activity within the posterior portion of the parahippocampal gyri, in close correspondence with the parahippocampal place area (Epstein et al., 1999), was significantly enhanced when participants viewed images of previously visited locations at which consistently negative events had been encountered, relative to when the locations had been associated with positive images matched for arousal level or with emotionally neutral stimuli. This enhancement for negatively conditioned places was elicited automatically in the absence of any navigational or explicit emotion-related information during retrieval, because during scanning only static-place images from the previously encountered rooms were shown. Critically, we only analyzed activations associated with the trial period, during which participants viewed static images of room locations and before seeing the objects that belonged within them. The enhanced parahippocampal response therefore cannot be attributed to explicit associations between the objects and emotional events.

The parahippocampal cortex forms part of a network of medial-temporal and parietal regions that is thought to be involved in different types of spatial processing (Mullally & Maguire, 2011; Baumann et al., 2010; Ohnishi, Matsuda, Hirakata, & Ugawa, 2006; Ploner et al., 2000; Bohbot et al., 1998; Maguire et al., 1998). Its main function has been attributed to perceptual encoding and retrieval of place and scene information (Epstein, 2008). It has been shown that neural responses within the parahippocampal region are modulated by the behavioral relevance of visual objects at critical decision points during navigation (Janzen & van Turenout, 2004). Our findings show for the first time that the parahippocampal cortex also differentiates

the navigational relevance of places based on previously experienced emotional events. Notably, this effect does not seem to rely on an immediate or explicit association between emotional stimuli and locations, as the presentation of emotion-related stimuli in our paradigm was incidental to the object location task performed a day later in the scanner. Consistent with this conclusion, a post-experiment questionnaire confirmed that participants were unaware of any relationship between the rooms in the virtual environment and the affective stimuli with which they were paired.

Critically, although the IAPS pictures employed as affective stimuli in our study were presented exclusively during the initial learning phase of the task, the enhancement of parahippocampal activity was observed the next day, when participants performed an object location memory task while in the scanner. Our observation of enhanced activity in the parahippocampal gyri when participants viewed static snapshots from the negatively conditioned room might reflect strengthened representations of learned place information. In a previous study, we found that increased parahippocampal activity during encoding was predictive of more accurate memory-based navigation in the absence of affective events (Baumann et al., 2010). Neuropsychological data further emphasize the importance of the parahippocampal cortex in navigational processes. Damage in this region often results in severe topographical difficulties specifically related to problems with identifying and remembering scene and object information (Mendez & Cherrier, 2003; Epstein, Deyoe, Press, Rosen, & Kanwisher, 2001; Barrash, Damasio, Adolphs, & Tranel, 2000). Enhanced representations of places associated with negative experiences may enable an individual to navigate his or her environment more effectively, thereby avoiding potential dangers and threats. Indeed, previous studies have shown that parahippocampal activity is modulated by contextual associations elicited by a visual scene (Howard, Kumaran, Olafsdottir, & Spiers, 2011; Bar, Aminoff, & Schacter, 2008; Aminoff, Gronau, & Bar, 2007; Düzel et al., 2003), and the parahippocampal cortex has also been implicated in contextual fear conditioning (Rudy, 2009; Alvarez, Biggs, Chen, Pine, & Grillon, 2008).

The significant increase in parahippocampal activity found for negatively conditioned places was specific to the room that was consistently associated with negative events during learning. Positive stimuli, whether delivered under a constant or intermittent schedule during learning, had no effect on parahippocampal activation relative to neutral stimuli, although arousal levels were matched independently for positive and negative stimuli. Similar to previous studies that have shown memory enhancement for negative emotional stimuli (Schwarze et al., 2012; Keightley, Chiew, Anderson, & Grady, 2011; Humphreys, Underwood, & Chapman, 2010; Mickley Steinmetz, Addis, & Kensinger, 2010; Mickley & Kensinger, 2008), our finding suggests that affectively modulated

place memory is valence-specific. Our findings are also consistent with previous studies that have shown that the parahippocampal gyrus is specifically involved in the processing of negative emotional stimuli but not positive emotional stimuli (Aldhafeeri, Mackenzie, Kay, Alghamdi, & Sluming, 2012; Gosselin et al., 2006). Valence-specific effects may reflect a natural bias of emotion regulation networks toward automatic processing of threat-related information. Modulation of activity within the parahippocampal gyrus might be more important for negative stimulus events than for positive ones because the former are potentially threatening and thus have immediate survival value (Davis et al., 2011).

In our study, affective images were operationalized by means of the widely accepted two-dimensional model of emotions, which is based on the assumption that positive and negative affect can be attributed to activation in two basic motivational systems, appetitive and aversive (Lang, 1995; Lang et al., 1990). It is important to acknowledge, however, that other accounts of emotion have argued for the existence of a set of discrete, primary emotions (e.g., fear, anger, happiness, etc.) that are instantiated by dedicated neural systems (e.g., Panksepp, 2008, 2011; Ekman, 1992). On this view, particular negative (or even positive) emotions might be more effective modulators of parahippocampal activity than others. For example, fear might elicit stronger parahippocampal responses during place retrieval than sadness. To answer this question, in future studies place information could be paired with stimuli from narrower emotional categories than employed here. It would also be interesting to compare affective stimuli that vary in their modality of presentation (e.g., visual vs. auditory; Royet et al., 2000). In this context, however, it should be noted that there is considerable interindividual variability in affective and neural responses to specific emotional categories (Baumann & Mattingley, 2012).

Interestingly, the effect of a negatively conditioned location on parahippocampal activity elicited during later recall arose exclusively under a constant schedule of associated negative events. By contrast, learning under an intermittent (50%) schedule had no such effect on parahippocampal responses during object location retrieval. In fact, neural activity elicited by retrieval of locations in which affective stimuli were encountered only intermittently was comparable with that of the neutral baseline, in which no emotionally arousing events occurred. This implies that an enhanced parahippocampal representation at retrieval relies on stable associations between negative events and the locations in which these are encountered. Previous studies examining the effect of negative emotions on memory found that, although emotional arousal enhanced memory for central elements of the emotional event (e.g., a snake), memory for peripheral elements (e.g., a forest) are more likely to be forgotten (e.g., Kensinger, Garoff-Eaton, & Schacter, 2007; Loftus, 1979). In these studies, however, negative objects were not consistently associated with a specific back-

ground. It seems likely that only consistent coupling of emotional events with a particular background will lead to enhanced recall of the background itself. It is important to note that in the extreme case of PTSD, often just a single exposure to a highly arousing event is enough to cause long-lasting neurobiological and cognitive changes (Brohawn et al., 2010; Wessa et al., 2006). However, the intensity of emotional events that lead to PTSD is not comparable to the intensity of the stimulation protocols that are typically employed in experimental settings. Future studies should further investigate how event schedules and varying levels of arousal during learning of object location information influence activity within the parahippocampal cortex and related areas.

Modulation of parahippocampal activity by emotionally arousing negative events likely depends upon the prior involvement of the amygdala complex (Kilpatrick & Cahill, 2003). Previous studies have shown that emotionally arousing experiences elicit amygdala activity, which then initiates neurobiological processes that enhance the consolidation of recent memory traces within the medial-temporal lobe (Cahill & Alkire, 2003; McGaugh, 2002; McGaugh & Roozendaal, 2002; Cahill & McGaugh, 1998). In this study, we measured neural activity exclusively during the retrieval phase, after place learning associated with affective stimuli had been completed. It is perhaps not surprising therefore that we did not find significant amygdala activity for any of the place stimuli during scanning. A recent fMRI study that examined the influence of nociceptive stimuli on memory for neutral pictures also found no significant increase in amygdala activity during retrieval, despite evidence for enhanced activity in a number of other brain regions, including the parahippocampal gyrus (Schwarze et al., 2012). The affective salience of learned locations, although mediated via the amygdala during encoding and consolidation, is likely to be stored independently within the parahippocampal gyrus for later retrieval (Cahill & McGaugh, 1998; Packard, Cahill, & McGaugh, 1994). Previous studies have shown that the extent of amygdala activity elicited by emotional stimuli during encoding can be predictive of subsequent memory retrieval performance (Ritchey, Dolcos, & Cabeza, 2008; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Hamann et al., 1999; Cahill et al., 1996). In future work, it will be important to assess the time course of any likely contribution of the amygdala to place learning when affective stimuli, particularly those with a negative valence, are involved.

In conclusion, our findings demonstrate that parahippocampal place representations are modulated by the emotional salience of previously visited locations during active exploration of a novel environment. During navigation, we not only use visual landmarks to guide our behavior (Chan, Baumann, Bellgrove, & Mattingley, 2013; Yoder, Benjamin, & Taube, 2011) but also call upon affective experiences that provide implicit cues about potential risks associated with visiting locations at which negative

events occurred previously. Our results reveal that parahippocampal place memory is automatically enhanced for places consistently associated with negative affect. More broadly, our study demonstrates the significant influence of emotion on neural and behavioral memory processes during spatial navigation. Future studies should consider how other forms of relevant emotional events might modulate spatial coding during navigation.

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