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Equivalent activation of the hippocampus by face-face and face-laugh paired associate learning and recognition

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ABSTRACT

The human hippocampus is known to play an important role in relational memory. Both patient lesion studies and functional-imaging studies have shown that it is involved in the encoding and retrieval from memory of arbitrary associations. Two recent patient lesion studies, however, have found dissociations between spared and impaired memory within the domain of relational memory. Recognition of associations between information of the same kind (e.g., two faces) was spared, whereas recognition of associations between information of different kinds (e.g., face-name or face-voice associations) was impaired by hippocampal lesions. Thus, recognition of associations between information of the same kind may not be mediated by the hippocampus. Few imaging studies have directly compared activation at encoding and recognition of associations between same and different types of information. Those that have have shown mixed findings and been open to alternative interpretation. We used fMRI to compare hippocampal activation while participants studied and later recognized face-face and face-laugh paired associates. We found no differences in hippocampal activation between our two types of stimulus materials during either study or recognition. Study of both types of paired associate activated the hippocampus bilaterally, but the hippocampus was not activated by either condition during recognition. Our findings suggest that the human hippocampus is normally engaged to a similar extent by study and recognition of associations between information of the same kind and associations between information of different kinds.

1. Introduction

The hippocampus has been known for many years to play a critical role in declarative memory (e.g., Scoville & Milner, 1957), but debate remains over its precise contribution. One influential view is that the hippocampus is involved in relational memory, that is, in forming associations in memory between stimuli, and between stimuli and their context (Eichenbaum, 1994, 2004). Indeed, there is considerable evidence from functional-imaging studies of healthy individuals that the hippocampus is involved in relational memory (Cansino, Maquet, Dolan, & Rugg, 2002; Davachi, Mitchell, & Wagner, 2003; Giovanello, Schnyder, & Verfaellie, 2004; Jackson & Schacter, 2004; Kensinger & Schacter, 2006; Kirchhoff, Wagner, Maril, & Stern, 2000; Kirwan & Stark, 2004; Köhler, Crane, & Milner, 2002; Ranganath et al., 2003; Small et al., 2001; Sperling et al., 2003; Stark & Okado, 2003; Weis, Klaver, Reul, Elger, & Fernández, 2004; Zeineh, Engel, Thompson, & Bookheimer, 2003; for a review see Davachi, 2006). Furthermore, recent research has suggested that the hippocampus has a greater involvement in relational than non-relational memory. This includes evidence from functional-imaging studies (Cansino et al., 2002; Davachi et al., 2003; Eldridge, Engel, Zeineh, Bookheimer, & Knowlton, 2005; Fenker, Schott, Richardson-Klavehn, Heinze, & Duzel, 2005; Giovanello et al., 2004; Henke, Buck, Weber, & Wieser, 1997; Henke, Weber, Kneifel, Wieser, & Buck, 1999; Jackson & Schacter, 2004; Kensinger & Schacter, 2006; Kirwan & Stark, 2004; Ranganath et al., 2003; Staresina & Davachi, 2006; Woodruff, Johnson, Uncapher, & Rugg, 2005; Yonelinas, Hopfinger, Buonocore, Kroll, & Baynes, 2001; Yonelinas, Otten, Shaw, & Rugg, 2005, but see Stark and Squire, 2001a and Gold, Smith et al., 2006 for contrary findings) and from patient lesion studies (Aggleton et al., 2005; Barbeau et al., 2005; Bastin et al., 2004; Henke, Kroll et al., 1999; Holdstock et al., 2002; Holdstock, Mayes, Gong, Roberts, & Kapur, 2005; Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Mayes et al., 2004; Turriziani, Fadda, Caltagirone, & Carlesimo, 2004; Vargha-Khadem et al., 1997; but for contrary findings see Cipolotti et al., 2001, 2006; Gold, Hopkins, & Squire, 2006; Kartsounis, Rudge, & Stevens, 1995; Reed & Squire, 1997; Stark, Bayley, & Squire, 2002; Stark and Squire, 2003).

Is it the case though that encoding and retrieval of all arbitrary associations engage the hippocampus to a similar extent? In

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two of the patient studies cited above, dissociations were found between spared and impaired memory within the domain of relational memory, implying that encoding and retrieval of some arbitrary associations may not, in fact, require the hippocampus. Patient YR (Mayes et al., 2004) was impaired at recognizing associations between information of different kinds, including object-location, object-temporal-order, face-voice, picture-sound, and face-occupation associations, but she was unimpaired at recognizing face-face and word-word associations, consistent with the notion that recognition of associations between information of the same kind may not be dependent on the hippocampus. A similar pattern was reported for three young patients with bilateral hippocampal damage dating from early childhood (Vargha-Khadem et al., 1997), although others have reported contrary findings (Stark & Squire, 2003; Turriziani et al., 2004).

In contrast, functional-imaging studies have clearly shown that the hippocampus is activated by encoding and retrieval of a wide range of stimulus associations, including associations between information of the same kind; for example, word pairs, recognition of which has been shown to be spared by hippocampal lesions (Mayes et al., 2004; Vargha-Khadem et al., 1997). Very few imaging experiments, however, have directly compared activation at encoding or recognition of associations between information of the same kind and information of different kinds. Prince, Daselaar, and Cabeza (2005) found activation of a region in the middle of the hippocampus common to encoding and recognition of both word pairs and pairings of words with specific fonts, leading them to argue that the hippocampus plays a “general and fundamental” role in relational memory. Interestingly though, these authors report that activation in the anterior left hippocampus tended to be larger for word-font encoding than for word-word encoding, which they suggest may indicate a role for this region in cross-domain binding, although it could just reflect the use of unusual fonts in that condition (Prince et al., 2005). Consistent with this latter finding, Gottlieb, Uncapher, and Rugg (2010) found that encoding that resulted in successful subsequent source recognition produced greater right hippocampal activation when a study picture was presented in the context of an auditory word (auditory source) rather than in the context of a visual word (visual source). Gottlieb and colleagues argued that this finding was consistent with the proposal that has arisen from the patient-lesion literature that the hippocampus is engaged more by memory for associations between information of different kinds than for associations between information of the same kind (Mayes et al., 2004; Mayes, Montaldi, & Migo, 2007). It should be noted, however, that the findings of Gottlieb et al. (2010) are consistent with an alternative interpretation; that is, that the greater hippocampal activity in the auditory context condition reflects a modality effect because auditory information was only presented in that condition and not in the visual context condition (see Gottlieb et al., 2010). There is therefore some indication from functional-imaging studies that the hippocampus may be engaged more by encoding of associations between information of different kinds than by encoding of associations between information of the same kind, but the evidence is currently meager, somewhat mixed, and open to alternative interpretation.

We used fMRI to investigate this issue in the current study. Like Gottlieb and colleagues, we compared relational memory in a cross-modal (visual-auditory) and a within-modality (visual-visual) condition. Unlike them, we used associative recognition memory tasks based on those used in patient-lesion studies of hippocampal function (e.g., Mayes et al., 2004), rather than the source-memory paradigm, and investigated activation during both encoding and recognition. In our study, we compared activation of the hippocampus during intentional encoding and recognition of associations between information of the same kind (face-face pairs) and associations between information of different kinds (face-laugh pairs). Faces and laughs were chosen for two reasons: first, to extend the range of materials over which associative recognition has been investigated using fMRI, as very few studies have used auditory stimuli, and second, to examine any lateralization of memory-related hippocampal activity for non-verbal but also non-spatial materials. This is of interest because it has been argued that the right hippocampus is specialized for spatial memory (O’Keefe & Nadel, 1978), and yet recent functional-imaging studies have shown right lateralized hippocampal activation in response to new configurations of stimuli regardless of the spatial/non-spatial nature of the task (Duzel et al., 2003), as well as during encoding of individual patterns (Branco et al., 2006; Golby et al., 2001), faces (Kelley et al., 1998; Powell et al., 2005) and objects (Martin, Wiggs, & Weisberg, 1997). We might therefore expect activation of the right hippocampus by the non-spatial materials used in our study.

In summary, we compared activation of the hippocampus during intentional encoding and recognition of associations between information of the same kind (face-face pairs) and associations between information of different kinds (face-laugh pairs). We predicted that, if the hippocampus is engaged more by encoding and recognizing associations between information of different kinds, then activation will be higher during study and recognition of face-laugh than face-face pairs.

2. Methods

2.1. Subjects

Twelve healthy young volunteers (6 female, 6 male, age range 19–39 years, mean 23.6 years (SD 5.4)) took part in the study. All were right-handed according to self-report. None of the subjects had a history of neurological illness and all had normal structural MRI scans. All subjects gave informed consent. The study was approved by the Montreal Neurological Institute and Hospital Research Ethics Board.

2.2. Stimuli

A total of 149 colored photographs of faces were used (106 male and 43 female). The faces were acquired from various sources: the AR Face Database (Martinez & Benavente, 1998); the Markus Weber collection at the California Institute of Technology (www.vision.caltech.edu/Image_Datasets); the CVL face database (CVL and CV, PTER, Velenje); and the NimStim Face Stimulus Set.[1]

All faces were processed so that only the neck, face and hair were visible and the background to the photograph was plain white. Care was taken to select faces for each stimulus set so that non-facial features, such as whether or not the individual was wearing spectacles, the illumination of the photograph, or the size of the face in the image, could not be used to aid performance on the recognition test. The faces were presented on a front-projection screen and viewed from within the scanner, using an angled mirror.

A total of 51 distinct laughs were selected from a database of natural laugh recordings collected by Jo-Anne Bachorowski (36 male and 15 female). The laughs were presented through MR compatible headphones. The volume at which the laughs were presented was determined by piloting prior to the study. This involved presenting the face-laugh task to participants whilst they were being scanned, and manipulating the volume of the laughs until participants were able to discriminate successfully between them, but without the volume being uncomfortably high. This volume was used for the actual experiment. In addition, in the actual experiment we asked each participant, after the first scanning run, whether the volume was comfortable and sufficient to discriminate between the laughs. None of the participants reported being unable to discriminate between the laughs.

2.3. Task design and procedure

A blocked design was used to investigate the involvement of the hippocampus during study and recognition of face-face and face-laugh paired associates. This design enabled us to achieve a higher signal-to-noise ratio and required less scanning time than an event-related design. Behavioral piloting showed that learning face-face and face-laugh pairings was difficult; thus, to maximize recognition perfor-

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[1] Development of the MacBrain Face Stimulus Set was overseen by Nim Tottenham and supported by the John D. and Catherine T. MacArthur Foundation Research Network on Early Experience and Brain Development. Please contact Nim Tottenham at tott0006@tc.umn.edu for more information concerning the stimulus set.

mance for both conditions, we used short study lists (7 stimulus pairs) and presented each study list three times before recognition was tested.

The design, shown schematically in Fig. 1, comprised six scanning runs (8.25 min each), during which three study blocks and one recognition block were acquired for each of the two experimental conditions (face-face and face-laugh pairings). Each scanning run included three 42 s study blocks and one 42 s recognition block for one experimental task. Successive study blocks were separated by a 15 s period of fixation. A 15 s period of distraction (odd/even judgment task, described below) was inserted between the final study block and the recognition test. The recognition block was followed by a 15 s period of fixation, after which the three 42 s study blocks for the other experimental task were presented, separated by fixation as before. Then, after a 15 s period of distraction (odd/even task), the 42 s recognition block for the second task was presented, followed by a 42 s block of trials that controlled for the low-level perceptual and motor aspects of the task (perceptual baseline, described below). Each task was preceded by brief written instructions (e.g., “face-face study”, “fixate”, “memory test”), which were presented for 2 s. The order of the two experimental tasks was counterbalanced over the scanning runs and over participants. The order in which the six sets of stimuli were used was counterbalanced over participants. Within a scanning run, the gender of all stimuli was held constant (i.e., either all male or all female).

During the face-face paired-associate study blocks, two different faces were presented on either side of the center of the screen. The faces remained on the screen for 5 s and there was a 1 s interval before the presentation of the next pair. A block comprised a total of 7 different pairs, each presented once. Participants were instructed to try to remember the pairings of faces for a later memory test (i.e., encoding was intentional). To aid encoding, on each trial, the participants indicated with a button press whether or not they considered the two faces to go well together (e.g., whether the individuals looked as if they could be from the same family or would get on well together). Simultaneous with the presentation of each face pair, a laugh was presented through headphones. The gender of the faces and the laugh were compatible (i.e., female faces with a female laugh). The same laugh was presented on all trials, and participants were instructed to ignore it; this controlled for early perceptual processing of the laugh recordings in the face-laugh condition. It will be referred to as the “filler laugh”.

The face-face paired-associate recognition block involved the presentation of the face pairs and laugh in an identical manner to the study blocks. However, only five of the face pairs were paired in the same way as at study; the other two were recombined. For each trial, participants indicated with a button press whether or not the faces were paired in the same way as at study.

During the face-laugh paired-associate study blocks, two different faces were presented on either side of the center of the screen. As in the face-face condition, the faces remained on the screen for 5 s, followed by a 1 s interval before the presentation of the next pair. A total of 7 pairs of same-gender faces were presented. Unlike the face-face condition, one face in each pair (that presented to the right of center) was the same on every trial, and participants were told that this picture was irrelevant to that task. This “filler face” was included to control for the low-level processing of two faces in the face-face condition. Simultaneous with the presentation of each face pair, a laugh was presented through headphones. As in the face-face condition, the gender of the faces and the laugh were compatible (i.e., female faces with a female laugh). Unlike the face-face condition, a different laugh was presented on each trial. Participants were instructed to associate each laugh with the face on the left of the screen and to remember the face-laugh pairings for a later memory test. To aid encoding of the face-laugh pairs, the participants indicated with a button press whether or not they considered that the face on the left of the screen and the laugh presented on that trial went well together.

The face-laugh paired-associate recognition block involved the presentation of the face pairs and laughs in an identical manner to the study block, but only five of the face-laugh pairings were the same as at study; the faces and laughs were recombined on the other two trials. For each trial, participants indicated with a button press whether or not the face on the left of the screen and the laugh were paired as at study.

So, in both experimental conditions, two faces and a laugh were presented on each trial. In the face-face condition, the subject’s attention was directed to the face-face pairings that had to be encoded or recognized, depending on the phase of the experiment, whilst the laughs were ignored; in the face-laugh condition, the subject’s attention was directed to the face-laugh pairings while the additional face was ignored. Thus, both visual and auditory information were presented in both conditions, but selective attention was directed to different aspects of the stimuli in the two conditions. Selective attention has been shown to influence what is encoded into a memory trace and to modulate hippocampal activity associated with source encoding, such that attended source-information that is successfully encoded elicits hippocampal activation, but unattended source-information does not (Uncapher & Rugg, 2009). We would therefore expect encoding and recognition of primarily face-face pairings in the face-face condition and of face-laugh pairings in the face-laugh condition and for hippocampal activation to reflect encoding and recognition of the attended stimulus pairings rather than unattended aspects of the stimulus array.

An odd/even distracter task was interposed between the final study block and the recognition test for each condition. Randomly generated numbers between 1 and 99 were presented in the centre of the screen for 1 s each and participants indicated with a button press whether the number was odd or even. This task was included to discourage rehearsal during the retention interval.

Each scanning run ended with a task (perceptual baseline), designed to control for the low-level perceptual processing of the visual and auditory stimuli and the motor processing related to making a button-press response in the experimental tasks. On each trial, the filler face was presented on both the left and right side of the screen for 5 s. The filler face was the one that was used in the face-laugh condition of that scanning run. The filler laugh from the face-face condition was presented simultaneously with the appearance of the faces. After a 1 s interval, the same faces and the same laugh were presented again. Participants were instructed to passively view the faces and listen to the laughs. In addition, they were instructed to make alternate button presses in response to each presentation of the stimuli (i.e., press the right button on the first presentation of stimuli, press the left button for the second presentation, press the right button for the third presentation, etc.). Thus, a motor response was made on each trial, but no judgment was required concerning the faces and laugh that were presented. As in the experimental tasks, there were 7 trials within the 42 s block. Activation during study and recognition blocks were compared with activation during this baseline to determine those brain regions that remained above threshold once activation associated with low-level perceptual processing of the visual and auditory stimuli, and with the motor processing involved in making a button press, had been subtracted out. Thus, these comparisons revealed regional activations during intentional encoding and recognition of paired associates over and above any activation associated with low-level perceptual and motor processing. We acknowledged that this baseline might engage the hippocampus to some small extent.

The odd/even distracter task that was used in the retention interval for each recognition task provided a second baseline against which we could compare study and recognition activations. It has been argued that hippocampally mediated memory processing is only minimally engaged by this task (Stark & Squire, 2001b). Thus, use of this baseline enabled us to examine hippocampal activation during study and recognition relative to a condition where hippocampal activity would have been minimal. The disadvantage of the odd/even baseline, and the reason why we also used the perceptual baseline, was that it did not control for the low-level perceptual/motor aspects of the tasks and so was likely to result in widespread cortical activations.

Participants underwent training on the tasks outside the scanner immediately prior to the scanning session. They then completed a full practice run within the scanner to acclimatize them to the scanning environment and give them further practice with both the tasks and the button box, before scanning commenced. This practice run comprised all tasks as they would occur during scanning, using a different set of stimuli with the exception of the filler face and laugh. The practice run was immediately followed by the six scanned runs.

2.4. Data acquisition

Data were acquired on a 1.5 Tesla Siemens Sonata scanner (Siemens, Erlangen, Germany) at the McConnell Brain Imaging Centre of the Montreal Neurological Institute (MNI). Functional images used a $T2^*$-weighted gradient-echo echo-planar (EPI) sequence for BOLD contrast with 4 mm × 4 mm in-plane resolution and 4 mm slice thickness. Perpendicular to the long axis of the hippocampus, 36 slices were collected every 0.085 s, resulting in an effective repetition time (TR) of 3.06 s/volume. For all subjects, a high-resolution 3D T1-weighted anatomical scan of the whole head with a 1 mm isotrophic resolution was also acquired. For three subjects, the structural scan was acquired before the functional scanning runs, for the other nine subjects it was acquired between the third and fourth sessions. The structural scans provided confirmation of the normal neurological status of our participants. These scans were also used to transform the functional images into the standard MNI space and were combined across all subjects to produce the average anatomical brain, used to localize the functional data.

2.5. Image analysis

Functional data were analyzed with fmristat (Worsley et al., 2002) implemented in Matlab 6.1 (Mathworks, Sherborne, MA, USA). Pre-processing included realignment, using the third frame of whichever scanning run yielded the smallest amount of rotation and displacement as the reference frame; this was the fourth scanning run for 10 of the 12 subjects and the third scanning run for the remaining 2 subjects. The data were also spatially smoothed using a 6 mm full-width half-maximum Gaussian kernel.

The data were analyzed using a blocked design. To produce the regressors of interest, nine boxcar functions were created (face-laugh first study block, face-laugh second study block, face-laugh third study block, face-laugh recognition, face-face first study block, face-face second study block, face-face third study block, face-face recognition, and perceptual control baseline) convolved with the canonical HRF. Frames with translations above 2 mm or rotations above 2 degrees were excluded from the analysis. Parameter estimates were calculated for each voxel.

The focus of our study was to determine whether there was greater activity in the hippocampus during face-laugh encoding and recognition than during face-face encoding and recognition. This primary question was investigated by computing

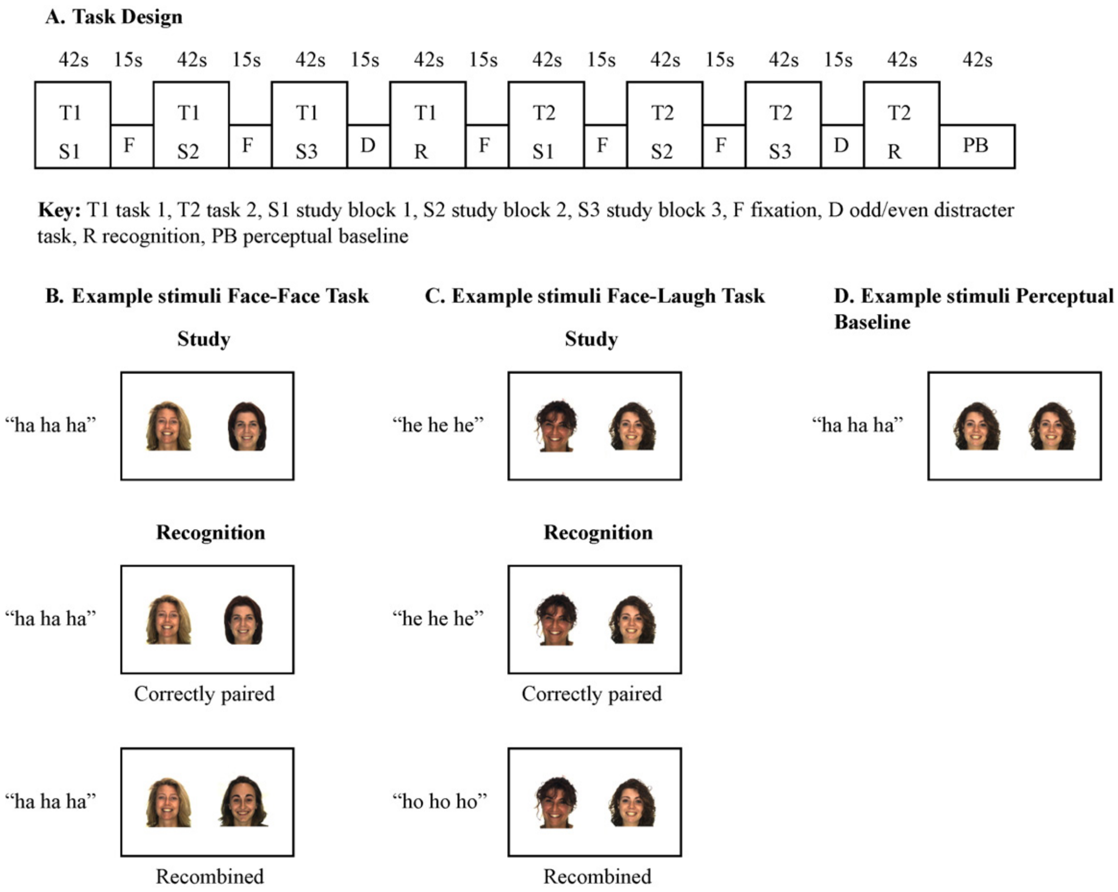

Fig. 1. Schematic illustration of the experimental design and sample stimuli. Panel A provides a schematic diagram illustrating one scanning run. Panel B shows sample stimuli from the study and recognition phases of the Face-Face condition. Panel C shows sample stimuli from the study and recognition phases of the Face-Laugh condition. Panel D shows sample stimuli from the perceptual baseline.

linear contrasts for each subject (fixed effects) to investigate the effect of face-laugh study versus face-face study and the effect of face-laugh recognition versus face-face recognition. In the event of finding no difference in hippocampal activation between conditions, we wanted to determine, as a supplementary question, whether or not the hippocampus had been activated by our tasks. To do this, linear contrasts were computed for each subject (fixed effects) to investigate the following effects: study (collapsed over task and study block) versus perceptual baseline; face-laugh study (combined over the 3 study blocks) versus perceptual baseline; face-face study (combined over the 3 study blocks) versus perceptual baseline; recognition (collapsed over task) versus perceptual baseline; face-laugh recognition versus perceptual baseline; face-face recognition versus perceptual baseline. In these comparisons, we were asking which brain regions were activated during intentional encoding and recognition of associative information, over and above any activity associated with the perceptual/motor processing required by the tasks. Although the perceptual baseline controlled for the low-level perceptual and motor aspects of the tasks, it may have engaged the hippocampus to some extent. So, to ensure that we detected any hippocampal activation, if present, we also obtained estimates of the main effects of study and recognition relative to the odd/even baseline in which the engagement of hippocampal memory processes has been shown to be minimal.

The parameter estimates were then used for the second-level analysis (mixed-effects) to examine effects across the whole group. For each contrast listed above, the parameter estimates for each subject were entered into a one-sample *t*-test. An undirected whole-brain analysis was conducted that identified activation that surpassed a threshold of $p < 0.001$, uncorrected. We report those clusters of activations that contained eight or more contiguous voxels and had a peak activation that survived correction for multiple comparisons across the whole brain, at $p < 0.05$.

To investigate activation within the hippocampus, we also used a hippocampal region-of-interest (ROI). This ROI was defined by delineating the border of the hippocampus, bilaterally, using the transformed (i.e., MNI space) structural scans. The delineation followed the method of Pruessner et al. (2000) and the hippocampal ROI included the dentate gyrus, the CA regions, the alveus and the fimbria. Activations are reported that fell within the hippocampal ROI and survived correction for multiple comparisons within the hippocampal ROI at a threshold of $p < 0.05$.

3. Results

3.1. Behavioral results

The mean proportion correct and the mean proportion of hits and false alarms for the two recognition tasks are shown in Table 1.

For each subject, the proportion of hits and false alarms for the face-laugh recognition task and that for the face-face recognition task (averaged over the 6 scanning runs) were converted to A' (Pollack & Norman, 1964) to obtain a bias-free measure of discrimination sensitivity. We were unable to use d' because a number of subjects obtained 100% hits and 0% false alarms. Performance levels on both tasks were high (mean A' of 0.89, SD = 0.062, and 0.94, SD = 0.066, for the face-laugh and face-face recognition tasks, respectively), indicating that participants were indeed successfully encoding both types of stimulus association. However, as can be seen from the mean A' scores, performance on the face-laugh recognition task was slightly lower than that on the face-face recognition task. The difference in performance was small (a mean difference in A' of 0.05), but it was found consistently over participants (11 of

Table 1
The mean proportion correct, mean proportion of hits and mean proportion of false alarms, with SD in parentheses, for the face-laugh and face-face paired associate recognition tasks.

	Proportion correct	Hits	False alarms
Face-laugh recognition	.849 (.081)	.903 (.086)	.271 (.155)
Face-face recognition	.915 (.080)	.931 (.077)	.125 (.149)

the 12 participants performed better on the face-face than the face-laugh task) and was therefore statistically significant (two-tailed t (11) = 2.540, $p = 0.027$). The same pattern of results was obtained when the analysis was repeated using the proportion correct (two-tailed t (11) = 3.326, $p = 0.007$) and the proportion of hits minus the proportion of false alarms (two-tailed t (11) = 2.887, $p = 0.015$) as the measures of performance.

4. fMRI results

4.1. Study phase

4.1.1. Face-laugh study versus face-face study

Activity in the hippocampus did not differ significantly between study of face-laugh and face-face stimulus pairs (threshold of $p < 0.001$, uncorrected). There were, however, a number of differences in the cortical-activation patterns between the two study tasks. Study of face-laugh stimulus pairs resulted in greater activation than study of face-face pairs in the following regions: bilateral superior, transverse and middle temporal gyri; bilateral inferior parietal lobule and postcentral gyrus; left supramarginal gyrus; bilateral inferior and medial frontal gyri; precentral gyri and paracentral lobule; bilateral insula; and bilateral posterior cerebellum (see Table 2). In contrast, study of face-face stimulus pairs resulted in greater activation than study of face-laugh pairs in the right middle and inferior frontal gyri and extensive areas of the occipital, temporal and parietal cortices bilaterally, including the fusiform gyrus (see Table 2).

4.1.2. Face-laugh and face-face study versus baselines

Relative to the perceptual baseline, we found significant bilateral activation of the hippocampus during study (collapsed over task and study block), at $p < 0.05$ corrected for multiple comparisons over the whole brain. Activation of the hippocampus was not, however, symmetrical. The cluster of activation in the right hippocampus (16 voxels) fell very centrally in the anterior region of the hippocampus, whereas the left hippocampal cluster (18 voxels) was more lateral and extended into the adjacent white matter. In Table 3, we show the co-ordinates of voxels within these two hippocampal clusters whose activation survived correction for multiple comparisons within the whole brain or within the hippocampal ROI at $p < 0.05$. Both clusters of activation remained significant in extent, corrected for multiple comparisons both within the whole brain and within the hippocampal ROI at $p < 0.05$.

As shown in Table 3 and Fig. 2, significant activation of the right and left hippocampus was also observed when the two study tasks were compared separately with the perceptual baseline. The comparison of face-laugh study and face-face study with the perceptual baseline revealed two clusters of hippocampal activation each, one in the left and one in the right hippocampus. As shown in Table 3, activation fell in similar locations for both tasks. All of these clusters of activation remained significant in extent, corrected for multiple comparisons both within the whole brain and within the hippocampal ROI at $p < 0.05$.

Using the odd/even baseline, which has been claimed to activate the hippocampus to a negligible degree (Stark & Squire, 2001b), but did not control for the low-level perceptual/motor aspects of the task, we observed increased activity in both the anterior and posterior hippocampus, bilaterally, at study (collapsed over task and study block). These activations formed part of an extensive cluster of 715 voxels that extended bilaterally from occipital cortex through temporal cortex and into the hippocampus (peak co-ordinates for right anterior hippocampal activation: 26 −14 −16, $t = 6.06$; peak co-ordinates for left anterior hippocampal activation: −36 −20 −16, $t = 6.78$; peak co-ordinates for the right posterior hippocampal activation: 30, −34, −4, $t = 6.72$; peak co-ordinates for the left posterior hippocampal activation: −20 −32 −4, $t = 9.44$). These peak activations were all significant after correction for multiple comparisons within both the hippocampal ROI and the whole brain at $p < 0.05$.

A number of other brain regions were significantly activated during study relative to the perceptual baseline (see Table 4). These findings included extensive activation of regions along the ventral visual stream, as well as activation of frontal and parietal cortex, cingulate gyrus, caudate and pulvinar.

4.2. Recognition phase

4.2.1. Face-laugh recognition versus face-face recognition

There were no significant differences in activation in the hippocampus or more generally in the medial temporal lobe between face-laugh and face-face paired-associate recognition (threshold of $p < 0.001$, uncorrected). As at study, activity in a number of cortical regions discriminated between recognition of face-laugh and face-face paired associates. Face-laugh recognition produced significantly greater activation than face-face recognition in bilateral superior, transverse and middle temporal gyri, left inferior parietal lobule, right postcentral gyrus, left inferior and middle frontal gyri, bilateral insula, cingulate gyrus and right posterior cerebellum (see Table 5 for peak co-ordinates). In contrast, there was greater activation in extensive areas of the occipital, temporal and parietal lobes, as well as bilateral posterior cerebellum and right anterior cerebellum, during face-face than face-laugh recognition. Peak co-ordinates for these activations are shown in Table 5.

4.2.2. Face-laugh recognition and face-face recognition versus baselines

There was no evidence of increased activation in the hippocampus during recognition of face-laugh and face-face paired associates, relative to the perceptual baseline, whether collapsed over task or for each task individually (corrected for multiple comparisons in the hippocampal ROI). To rule out the possibility that the absence of hippocampal activation was due to engagement of hippocampal processing by the perceptual baseline task, the analysis was repeated with the odd/even baseline, during which there is minimal engagement of the hippocampus. Recognition produced no significant increases in activation relative to this baseline, corrected for multiple comparisons in the hippocampal ROI. We also examined recognition, relative to each baseline, without correcting for multiple comparisons (threshold $p < 0.001$, uncorrected). Relative to the perceptual baseline, there was one cluster of activation in the right hippocampus, but this comprised only a single voxel (coordinates 22 −18 −20, $t = 3.94$) and was absent in the comparison with the odd/even baseline, which showed no regions of activation within the hippocampus. We also found no evidence of increased activation in other regions of the medial temporal lobe during recognition relative to either the perceptual or the odd/even baseline, whole-brain corrected.

Outside the medial temporal lobe, recognition produced significantly more activation than the perceptual baseline in a number of regions. These regions included: extensive areas of the occipital, temporal, and parietal cortex bilaterally; bilateral superior, middle, inferior and medial frontal gyri; left precentral gyrus; right insula and caudate; and bilateral thalamus, cingulate gyrus and posterior cerebellum (see Table 6).

5. Discussion

5.1. Hippocampus and the medial temporal cortex

We found that the hippocampus was activated bilaterally by the intentional study of face-face stimulus pairs and face-laugh stim-

Table 2
Brain regions activated more by (a) study of face-laugh than study of face-face paired-associates, and (b) study of face-face than study of face-laugh paired-associates, at a threshold of $p < 0.001$, uncorrected, and whose peak activation survived correction for multiple comparisons across the whole brain at $p < 0.05$. For each cluster we show the number of activated voxels and either peak coordinates of the cluster or, for large clusters, the peak coordinates of each activated brain region within the cluster.

	No. of voxels	Coordinates			*t*
		x	*Y*	*z*	
Face-Laugh > Face-Face					
Left temporal/parietal/frontal	206				
Temporal lobe					
Superior temporal gyrus		−58	−14	6	14.72
Transverse temporal gyrus		−58	−20	12	11.7
Middle temporal gyrus		−62	−36	4	6.70
Parietal lobe					
Inferior parietal lobule		−66	−32	24	10.09
Supramarginal gyrus		−54	−48	36	8.87
Post central gyrus		−64	−22	18	7.69
Frontal lobe					
Inferior frontal gyrus		−48	24	0	7.83
Precentral gyrus		−56	10	12	6.34
Insula		−50	−34	20	8.66
Right temporal/parietal/frontal	203				
Temporal lobe					
Superior temporal gyrus		64	−12	0	15.94
Transverse temporal gyrus		48	−26	12	7.14
Middle temporal gyrus		62	−4	−4	9.46
Parietal lobe					
Inferior parietal lobule		48	−32	22	8.46
Post central gyrus		58	−22	16	8.78
Frontal lobe					
Inferior frontal gyrus		54	16	−4	9.20
Precentral gyrus		64	−2	10	6.62
Insula		58	−34	20	7.42
Right frontal	26				
Medial frontal gyrus		0	−20	48	8.85
Paracentral lobule		0	−18	46	7.70
Left cerebellum	14	−22	−80	−34	7.70
Right cerebellum	19	14	−78	−30	6.70
Face-Face>Face-Laugh					
Occipital/temporal/parietal/cerebellum	362				
Right occipital lobe					
Lingual gyrus		8	−84	2	28.02
Cuneus		10	−78	8	21.79
Middle Occipital gyrus		46	−80	2	17.28
Fusiform		30	−72	−14	15.41
Superior Occipital gyrus		36	−78	30	14.26
Inferior Occipital gyrus		28	−90	−6	9.23
Right temporal lobe					
Inferior temporal gyrus		48	−74	−2	15.63
Fusiform gyrus		40	−60	−14	13.82
Middle temporal gyrus		44	−76	12	10.91
Angular gyrus		48	−70	30	8.62
Parahippocampal gyrus		30	−54	−6	9.98
Right parietal lobe					
Superior parietal lobule		30	−58	48	10.20
Precuneus		28	−64	34	10.80
Inferior parietal lobule		36	−50	56	6.95
Posterior cingulate		24	−68	6	11.29
Cerebellum (posterior)		8	−76	−12	26.47
Cerebellum (anterior)		10	−68	−6	13.06
Left occipital lobe					
Lingual gyrus		−12	−56	2	8.81
Cuneus		−12	−70	14	8.62
Middle Occipital gyrus		−42	−64	−10	15.50
Fusiform		−38	−72	−14	16.84
Superior Occipital gyrus		−32	−84	22	7.99
Inferior Occipital gyrus		−42	−70	−4	13.75

Table 2 (*Continued*)

	No. of voxels	Coordinates			*t*
		x	*Y*	*z*	
Left temporal lobe					
Fusiform gyrus		−46	−50	−12	7.55
Middle temporal gyrus		−32	−76	20	7.91
Parahippocampal gyrus		−10	−48	4	6.05
Left parietal lobe					
Superior parietal lobule		−36	−54	52	8.05
Precuneus		−26	−58	52	7.51
Inferior parietal lobule		−40	−38	44	7.18
Posterior cingulate		−16	−56	6	7.52
Right Middle frontal gyrus	15	30	−4	58	6.32
Right Inferior frontal gyrus	17	50	6	30	7.86

ulus pairs and that activation did not differ significantly between these two conditions. We also found no difference in hippocampal activation between our two types of stimuli during recognition, which (unlike the study phase) did not result in hippocampal activation relative to either baseline in our study. Our findings, therefore, suggest that the human hippocampus is normally engaged to a similar extent by study or recognition of associations between items of the same or different types. Below, we discuss in more detail the patterns of activation in the hippocampus and medial temporal lobe during study and recognition, before briefly considering activations obtained in other brain regions.

5.2. *Study phase*

Previous fMRI studies have shown that the hippocampus is activated by encoding of associations between information of different kinds, such as face-name pairs (Kirwan & Stark, 2004; Small et al., 2001; Sperling et al., 2003) and word-color pairs (Staresina & Davachi, 2006) and by encoding of associations between memoranda of the same kind (Jackson & Schacter, 2004). However, only a few studies (Gottlieb et al., 2010; Prince et al., 2005) have directly compared hippocampal activation related to encoding of associations between information of the same kind and of associations between information of different kinds, and these studies have produced mixed results. Prince and colleagues found activation of a region in the middle of the hippocampus common to encoding and recognition of both word pairs and pairings of words with specific fonts, suggesting that the hippocampus was involved in encoding and recognition of both types of stimulus association. However, they also note that activation of the anterior left hippocampus tended to be larger for word-font encoding than for word-word encoding, which could reflect greater involvement of this region in cross-domain binding (Prince et al., 2005). Gottlieb et al. (2010) also report findings consistent with this view that the hippocampus may be engaged more during encoding of different types of information. They found greater right hippocampal activation by successful source encoding when the source was presented in a different modality (auditory source) relative to the same modality (visual source). In contrast to Gottlieb et al. (2010), the findings of our study, which also compared study of visual-visual and visual-auditory associations, showed equivalent activation of the hippocampus during study of information of the same kind (face-face associations) and study of information of different kinds (face-laugh associations). Our findings are therefore

Table 3

The number of voxels, coordinates and the value of *t* for two clusters of activation, one in the right and the other in the left hippocampus, produced by study of face-laugh and face-face associations relative to the perceptual baseline significant in extent and height at $p < 0.001$, uncorrected. In the table we show the coordinates of all activated voxels in these clusters that survived correction for multiple comparisons within the hippocampal ROI at $p < 0.05$.

	Right hippocampus					Left hippocampus				
	No. of voxels	Coordinates			*t*	No. of voxels	Coordinates			*t*
		x	*y*	*z*			*x*	*y*	*z*	
Study vs perceptual baseline	16	22	−16	−18	6.37**	18	−32	−12	−24	6.37**
		22	−18	−20	5.67**		−32	−10	−26	4.72*
		22	−14	−16	4.75*		−30	−8	−26	4.66*
		22	−12	−14	4.71*		−32	−14	−22	4.44*
							−32	−4	−14	4.43*
							−28	−6	−24	4.30*
							−36	−8	−28	3.93*
Face-Laugh study vs perceptual baseline	21	24	−18	−20	5.48*	19	−32	−12	−24	5.97**
		22	−16	−18	5.46*		−32	−10	−26	5.11*
		20	−12	−14	4.63*					
		22	−14	−12	4.54*					
		24	−12	−10	4.34*					
		28	−20	−20	4.18*					
Face-Face study vs perceptual baseline	20	24	−18	−20	4.39*	14	−32	−12	−24	5.25*
		28	−20	−20	4.27*		−32	−10	−26	4.85*
		26	−16	−18	4.17*		−32	−14	−22	4.46*
		22	−14	−18	4.16*		−36	−8	−28	4.43*
		20	−12	−14	4.10*					
		22	−12	−20	4.07*					

[*] Indicates that the activation was significant in height corrected for multiple comparisons within the hippocampal ROI at $p < 0.05$.

[**] Indicates that the activation was also significant in height corrected for multiple comparisons over the whole brain at $p < 0.05$.

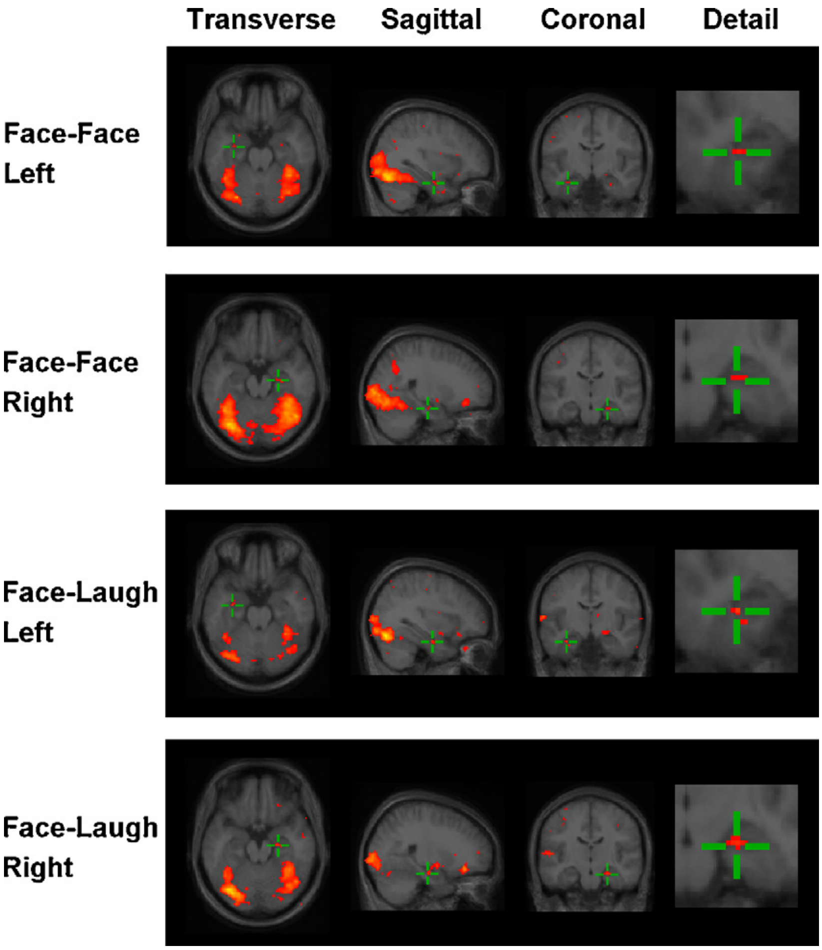

Fig. 2. Activation of the left and right hippocampus during intentional study of face-face and face-laugh paired-associates relative to the perceptual baseline. The activation is shown on transverse, sagittal and coronal slices at MNI co-ordinates −32 −12 −24 (left hippocampus) and 24 −18 −20 (right hippocampus). The final image in each row shows a magnified image of the coronal slice centered on the crosshair. All hippocampal activations shown are at $p < 0.05$, small volume corrected.

consistent with those of Prince et al. (2005) that the hippocampus is commonly activated by encoding of between- and within-domain associations, as predicted by the view that it plays a general role in relational memory (Eichenbaum, 1994, 2004), but inconsistent with the findings of Gottlieb et al. (2010).

There are a number of reasons why our findings may have differed from those of Gottlieb et al. (2010). First, Gottlieb et al. (2010) suggested that the difference in hippocampal activation between their conditions may not be due to encoding of within- and across-modality associations, but rather may be explained by a modality effect related to the use of auditory stimuli only in the auditory source condition. Second, although both studies contrasted visual-visual and visual-auditory associations, both the materials (object pictures and visually or auditorily presented words in Gottlieb et al. (2010), and face pairs or face-laugh pairs in our study) and the paradigm (incidental encoding using a source memory paradigm versus intentional encoding using an associative recognition paradigm) differed. In addition, the design of the two studies differed. Gottlieb et al. (2010) used an event-related subsequent memory design, so the difference they report was between successful encoding of same and different modality source memory. In contrast, we used a blocked design, which averaged over both successfully and unsuccessfully encoded associations, so that we were looking at activation related to intentional study of the two types of stimulus association rather than activation specifically associated with successful encoding. Although recognition performance was high in our study and thus activation observed during the study phase will be primarily related to successful rather than unsuccessful encoding, we cannot rule out the possibility that subtle differences would be present if only successfully encoded trials were considered. Further work is required to explore these differences and determine whether, and, if so, under what conditions, encoding of associations between same and different types of information engage the hippocampus to a different extent.

It could be argued that we did not obtain a difference in hippocampal activation between study of face-face and face-laugh pairs because of incidental face-laugh encoding in the face-face study task. This could potentially occur because a repeated laugh was presented together with the face pairs on each trial. This interpretation is based on the view of Moscovitch (2008), who proposes that the hippocampus is "stupid" and encodes all information of which the individual is conscious. However, this view has been recently challenged by a study that showed that selective attention modulated hippocampal activation associated with successful source-encoding (Uncapher & Rugg, 2009). These researchers presented pictures that had different-colored frames, in different locations on the screen. In the location condition, location of the picture determined the judgment that had to be made about the picture, whereas in the color condition, color of the frame determined the judgment that had to be made. So, the stimulus array included both color and location information, but attention was directed to different information in the two conditions. They found hippocampal subsequent-memory effects for color and location source-features according to which feature attention was directed.

Table 4
Brain regions, excluding the hippocampus, activated significantly more by study (collapsed over condition) than by the perceptual baseline, at a threshold of $p < 0.001$, uncorrected, and whose peak activation survived correction for multiple comparisons across the whole brain at $p < 0.05$. For each cluster we show the number of activated voxels and either peak coordinates of the cluster or, for large clusters, the peak coordinates of each activated brain region within the cluster.

	No. of voxels	Coordinates			*t*
		x	*y*	*z*	
Occipital/temporal/cerebellum	198				
Occipital					
Right inferior occipital gyrus		12	−92	−8	17.61
Left inferior occipital gyrus		−16	−90	−10	14.58
Right middle occipital gyrus		38	−72	−12	13.28
Left middle occipital gyrus		−20	−88	−12	15.63
Right fusiform gyrus		42	−82	0	14.65
Left fusiform gyrus		−36	−92	−8	12.03
Right lingual gyrus		20	−78	−14	10.16
Left lingual gyrus		−8	−92	−14	13.99
Right cuneus		26	−96	2	11.29
Left cuneus		−22	−98	0	9.16
Temporal					
Right fusiform gyrus		38	−50	−16	12.80
Right inferior temporal gyrus		48	−70	0	7.47
Right anterior cerebellum		34	−50	−18	12.77
Right posterior cerebellum		38	−68	−16	12.20
Left anterior cerebellum		−40	−52	−22	10.02
Left posterior cerebellum		−32	−76	−18	15.92
Parietal	25				
Right precuneus		32	−70	40	8.42
Right superior parietal lobule BA7		36	−72	44	5.66
Right middle frontal gyrus	52	42	30	20	9.00
Right middle frontal gyrus	33	24	32	−12	7.86
Superior frontal gyrus	38	0	16	50	8.24
Left frontal	46				
Left inferior frontal gyrus		−40	24	−10	7.99
Left middle frontal gyrus		−42	36	16	7.66
Left precentral gyrus	42	−34	−20	48	5.79
Right extranuclear white matter extending into putamen and midbrain	16	20	−4	−10	7.00
Left amygdala/parahippocampal	18				
Left amygdala		−18	−6	−12	8.50
Left white matter/putamen and parahippocampal gyrus		−22	−6	−8	7.99
Left head of caudate	19	−14	14	4	6.58

That is, encoding-related hippocampal activity was associated with the attended but not unattended source-feature. This led them to argue that "..the hippocampus does not simply encode the totality of the available contextual information, but rather the subset of information that is most behaviorally relevant" (Uncapher & Rugg, 2009). The findings of this recent study, therefore, lead us to expect that in our face-face condition, in which the participants' attention is directed to the task-relevant face-face pairings, and away from the irrelevant repeated laugh, hippocampal activation will reflect encoding of the attended face pairs rather than encoding of the unattended, and task irrelevant, association between the face pairs and the repeated laugh. Furthermore, the pattern of cortical activations obtained in our study suggests that participants were indeed attending to different information in our two study conditions. Corbetta, Miezin, Dobmeyer, Shulman, and Petersen (1990) have argued that selective attention enhances activity in the cortical regions engaged in processing the attended information. In support of this view, Uncapher and Rugg (2009) showed that selective attention affected activity in the regions involved in processing color and location information, such that activity in right parahippocampal gyrus and left peristriate cortex (V4) was associated with attention to color-source information and activity in right superior parietal cortex was associated with attention to location-source information. In our study, intentional study of face-laugh pairings (face-laugh study condition) resulted in greater activation of auditory cortex (superior temporal and transverse gyri), and other regions involved in auditory processing, such as the inferior parietal gyrus and inferior frontal gyrus (Poremba & Mishkin, 2007), as well as the insula, which has been associated with laugh perception (Sander, Brechmann, & Scheich, 2003; Sander & Scheich, 2001, 2005), than did intentional study of face-face pairs; this was the case even though a laugh was presented on each trial during the face-face study condition. This cortical activation therefore suggests greater attention to the laughs during the face-laugh than the face-face condition. In contrast, the face-face study condition produced greater activation in the ventral visual processing stream than the face-laugh study condition, consistent with attention being directed to the visual stimuli and the associated engagement of the visual-processing areas in the face-face study condition.

In summary, we found equivalent hippocampal activation during study of face-laugh and face-face paired associates. Our data suggest that the hippocampus is normally engaged during intentional study of both types of associations.

5.3. *Recognition phase*

As with the study phase, recognition of face-face and face-laugh paired associates produced no significant differences in hippocampal activation. There was, therefore, no indication that

Table 5

Brain regions activated significantly more by (a) recognition of face-laugh than recognition of face-face paired-associates, and (b) recognition of face-face than recognition of face-laugh paired-associates, at a threshold of $p < 0.001$, and whose peak activation survived correction for multiple comparisons across the whole brain at $p < 0.05$. For each cluster we show the number of activated voxels and either peak coordinates of the cluster or, for large clusters, the peak coordinates of each activated brain region within the cluster.

	No. of voxels	Coordinates			*t*
		x	*y*	*z*	
Face-Laugh>Face-Face					
Left temporal/parietal/frontal	106				
Temporal lobe					
Superior temporal gyrus		−64	−26	2	8.94
Transverse temporal gyrus		−62	−16	10	7.30
Middle temporal gyrus		−58	−48	8	7.17
Inferior parietal lobule		−66	−38	26	6.17
Inferior frontal gyrus		−52	26	−6	6.15
Insula		−46	−38	18	5.91
Right temporal/parietal	93				
Temporal lobe					
Superior temporal gyrus		64	−28	8	8.59
Transverse temporal gyrus		56	−18	10	6.53
Middle temporal gyrus		56	−22	−4	7.87
Post central gyrus		68	−20	16	6.83
Insula		56	−32	18	6.34
Left frontal	14				
Inferior frontal gyrus		−48	12	18	5.79
Middle frontal gyrus		−48	12	30	6.92
Cerebellum (posterior)	8	16	−80	−36	5.84
Face-Face>Face-Laugh					
Right occipital/temporal/parietal/cerebellum	222				
Occipital					
Lingual gyrus		8	−88	2	16.54
Middle occipital gyrus		32	−80	20	11.70
Fusiform		40	−72	−12	11.23
Inferior occipital gyrus		36	−76	−6	8.95
Cuneus		12	−86	10	8.75
		8	−88	20	5.91
Temporal lobe					
Middle temporal gyrus		32	−74	20	9.31
Fusiform		40	−54	−14	8.65
Inferior temporal gyrus		52	−64	−2	8.43
Parahippocampal gyrus		28	−52	−6	6.53
Parietal lobe					
Superior parietal		26	−62	52	8.18
Precuneus		24	−70	42	6.85
Cerebellum (posterior)		22	−74	−14	14.91
Cerebellum (anterior)		34	−48	−18	6.39
Left occipital/temporal/cerebellum	85				
Occipital		−30	−70	−10	6.14
Lingual gyrus		−44	−78	2	7.82
Middle occipital gyrus		−32	−74	−14	6.49
Cuneus		−6	−76	36	6.53
Inferior temporal gyrus		−44	−66	0	6.18
Cerebellum (posterior)		34	−58	−16	5.83

the hippocampus was more involved in recognition of one type of stimulus association than the other. For both material types, we found no evidence for an increase in hippocampal activation associated with recognition. Recognition, collapsed over task, did not activate the hippocampus significantly relative to either our perceptual or odd/even baselines. It is perhaps unsurprising that we did not observe hippocampal activation for the comparison with the perceptual baseline, which involved repeated presentation of an over-learned face and laugh, because the perceptual baseline itself may have triggered recognition and therefore may have also activated the hippocampus, thus reducing the chance of observing recognition-related activity in this comparison. Similarly, the perceptual baseline may have triggered hippocampal activation associated with encoding the association between the over-learned face and laugh, which were encountered together for the first time in this condition. However, such explanations cannot account for the lack of activation relative to the odd/even baseline, which has been said to activate the hippocampus to a negligible extent (Stark & Squire, 2001b).

It was also not the case that the length of scanning time used at recognition was insufficient, per se, to detect hippocampal activation. The same amount of scanning time during the study phase

Table 6
Brain regions activated significantly more by recognition, collapsed over task, than the perceptual baseline, at a threshold of $p < 0.001$, and whose peak activation survived correction for multiple comparisons across the whole brain at $p < 0.05$. For each cluster we show the number of activated voxels and either peak coordinates of the cluster or, for large clusters, the peak coordinates of each activated brain region within the cluster.

	No. of voxels	Coordinates			*t*
		x	*y*	*z*	
Occipital/temporal/cerebellum	217				
Right occipital lobe					
Fusiform gyrus		38	−70	−14	11.44
Inferior occipital gyrus		14	−90	−8	17.89
Lingual gyrus		14	−94	−4	12.01
Middle occipital gyrus		32	−92	4	12.48
Cuneus		26	−94	2	12.13
Right temporal lobe					
Fusiform		38	−50	−16	10.64
Middle temporal		68	−32	−10	9.02
Precentral gyrus		34	20	34	6.39
Right cerebellum (posterior)		16	−76	−24	7.82
Left occipital lobe					
Fusiform gyrus		−20	−88	−12	18.71
Inferior occipital gyrus		−16	−90	−10	14.70
Lingual gyrus		−4	−94	−6	14.08
Middle occipital gyrus		−28	−94	8	10.60
Cuneus		−12	−98	−2	8.46
Left fusiform		−48	−66	−14	7.10
Left cerebellum (posterior)		−36	−72	−20	19.29
Parietal lobe	107				
Right inferior parietal		38	−56	46	11.46
Right precuneus		32	−70	40	11.16
Right superior parietal lobule		40	−58	50	9.26
Right angular gyrus		36	−56	34	7.84
Right postcentral gyrus		44	−22	52	5.75
Left inferior parietal		−40	−46	40	7.05
Left precuneus		−12	−64	36	6.44
Left superior parietal lobule		−32	−66	52	6.68
Frontal lobe and medial structures	183				
Right middle frontal gyrus		44	32	24	12.57
Right inferior frontal gyrus		44	22	−4	9.13
Right insula		32	24	2	8.68
Right caudate		14	6	18	6.48
Right thalamus		10	−12	10	6.36
Left thalamus		−4	−16	12	6.19
Left frontal lobe	87				
Left middle frontal gyrus		−44	36	16	10.76
Left inferior frontal gyrus		−38	26	0	9.70
Precentral gyrus		−42	2	36	6.87
Claustrum		−28	20	−2	6.04
Frontal lobe/cingulate	58				
Right superior frontal gyrus		4	14	54	9.09
Right medial frontal gyrus		4	28	46	11.00
Right cingulate gyrus		4	24	40	7.76
Left superior frontal gyrus		−2	12	56	8.21
Left medial frontal gyrus		−2	34	38	7.41
Left cingulate gyrus		−10	28	28	5.69
Cingulate gyrus	10				
Right cingulate		2	−34	30	10.72
Left cingulate		−4	−34	28	8.54
Left cerebellum (posterior)	17	−34	−74	−42	7.13

revealed significant hippocampal activation. Study phase 1 (averaged over the face-face and face-laugh tasks) was based on the same amount of scanning time/trials as the recognition phase (averaged over the face-face and face-laugh tasks), that is, two blocks of 42 s scanning per scanning run. Yet, in contrast to the recognition phase, study phase 1 produced significant activation in the hippocampus relative to the perceptual control baseline (peak activations 24 −18 −20, $t = 5.25$, −32 −12 −24, $t = 5.20$, both significant corrected at $p < 0.05$ for multiple comparisons within the hippocampal ROI) and relative to the odd/even baseline (peak activations 26 −20 −16, $t = 6.56$, −26 −14 −20, $t = 6.05$, both significant corrected at $p < 0.05$ for multiple comparisons over the whole brain).

One possible explanation for our negative finding may relate to the limitation of using a blocked design. This design combines activations for hits, misses, false alarms and correct rejections, and thus we cannot rule out the possibility that activation of the hippocampus related to successful recognition was not detected, because it was combined with lower activation associated with the other categories of response. It should, however, be noted that the recognition test was designed such that recognition lists consisted predominantly of correctly paired stimuli (5/7 trials per block—71%) and that performance was high, so that the majority of trials in each block were hits (the mean numbers of hits, false alarms, correct rejections and misses, averaged over all participants and the 6 scanning runs, were 27, 3, 3, 9 for the face-laugh recognition task and 28, 2, 2, 11 for the face-face recognition task). Therefore, activation related to correct recognition would be expected to predominate.

The most likely explanation of our findings is that the hippocampus is not activated during recognition under the specific set of circumstances in our study. This may be the case if the recollection processes associated with increased hippocampal activation in previous studies were not engaged by the recognition tasks used in our study, but rather that recognition of the paired associates was based on a process more akin to a sense of familiarity. Although associative recognition is generally considered to require recollection rather than just familiarity (see Yonelinas, 2002, for review), it has been recently shown that recognition of arbitrary associations between previously unrelated pairs of words can be mediated by familiarity in certain situations (Quamme, Yonelinas, & Norman, 2007). Quamme et al. (2007) showed that patients with deficits in recollection, but spared familiarity-judgment, following hypoxia, which was assumed to have resulted in relatively selective hippocampal damage, were better at recognizing pairs of words that were presented as novel compound words (unitized) than word pairs that were linked by a sentence in which they both appeared (non-unitized). Both healthy controls and patients with large medial temporal lesions and deficits in recollection and familiarity showed no advantage when the word pairs were unitized. Quamme et al. proposed that familiarity, mediated by cortical regions, supported the successful associative recognition of the unitized word-pairs of the hypoxic patients. It has also been argued that recognition of paired associates that have been repeatedly presented may depend less on hippocampally mediated recollection than paired associates that have only been experienced once (Zeineh et al., 2003). As with unitization of the associated information, it has been suggested that under these circumstances recognition may become more dependent on neocortical regions (Zeineh et al., 2003). Either, or perhaps both, of these possibilities could explain why, in our study, we did not find an increase in hippocampal activation during recognition. We used multiple learning trials, with paired associates presented three times before the recognition test. It is also plausible that participants could have adopted a strategy of unitizing the face-face and face-laugh pairs during the experiment, although this was not encouraged (or discouraged). If this were the case, then the possibility of using familiarity-based recognition of unitized associations might not only apply to associations between similar items (Quamme et al., 2007), but may extend to associations between certain types of information of different kinds (e.g., faces and voices) that could plausibly form a single unit.

In summary, we found no differences in hippocampal activity during a recognition test for face-laugh associations relative to a recognition test for face-face associations. We therefore found no evidence that the hippocampus was engaged to a different extent by recognition of the two types of stimulus associations. In the recognition phase of our study, no regions of increased activation in the hippocampus were observed. It remains for future work to determine whether hippocampal activity obtained during recognition of same and different item-associations remains equivalent under conditions that result in increased activation in the hippocampus (e.g., conditions that engage and isolate recollection).

5.4. *Comparison of our findings with the results of patient lesion studies*

Our findings appear to be consistent with the notion of equivalent impairments after bilateral hippocampal damage of face-face and face-occupation recognition (Turriziani et al., 2004) and object-object and face-house recognition (Stark & Squire, 2003). They are apparently inconsistent with the findings of sparing of face-face recognition but impaired recognition of associations between information of different kinds (Mayes et al., 2004; Vargha-Khadem et al., 1997). Nevertheless, it is possible that the hippocampus is normally involved in encoding both types of association, as the data from our study phase suggest, but that it is not necessary for both, and that recognition of face-face associations can also be supported by brain systems that do not involve the hippocampus (see Price & Friston, 2002, for a discussion of the notion of degeneracy of cognitive brain systems). For example, in non-human primates it has been shown that rhinal cortex supports recognition of associations between pairs of visually presented objects (Murray, Gaffan, & Mishkin, 1993), suggesting one candidate region that may be able to mediate recognition of associations between visual stimulus-pairs in humans. In our study, parahippocampal cortex and fusiform gyrus were activated more by face-face than face-laugh encoding, and these structures have previously been shown to be involved in encoding pictures of scenes by human subjects (Kirchhoff et al., 2000). These may be further candidate regions for supporting recognition memory for associations between face pairs.

5.5. *Lateralization of hippocampal activation*

We will now turn briefly to the question of lateralization of the hippocampal activation related to the encoding of non-verbal, but non-spatial materials, in our study. Clear activation of the right hippocampus by our encoding task is important because it has been argued that in humans the right hippocampus is specialized for spatial memory (O'Keefe & Nadel, 1978). The study of patients with left or right anterior temporal lobectomy has lent some support for this view (e.g., Pigott & Milner, 1993), but other patient studies have suggested that the right hippocampus is not limited to encoding spatial information (Cohn, McAndrews, & Moscovitch, 2009; Jones-Gotman, 1986; Smith & Milner, 1981). Indeed, recent functional-imaging studies have shown right lateralized activation associated with encoding individual patterns (Branco et al., 2006; Golby et al., 2001), faces (Kelley et al., 1998; Powell et al., 2005) and objects (Martin et al., 1997), as well as verbal stimuli under certain circumstances (Kennepohl, Sziklas, Garver, Wagner, & Jones-Gotman, 2007). In fact, Duzel et al. (2003) showed that the right anterior hippocampus was activated more by new than old configurations of stimuli, regardless of the spatial/non-spatial nature of the task. Activation of the right hippocampus by face-face and face-laugh encoding in our study is therefore consistent with these previous imaging studies and extends the range of materials over which encoding-related activation of the right hippocampus has been found. It also provides further evidence in support of Duzel et al.'s conclusion that the hippocampus encodes event information rather than spatial coordinates (Eichenbaum, 2001; Wood, Dudchenko, & Eichenbaum, 1999; Wood, Dudchenko, Robitsek, & Eichenbaum, 2000).

There are two possible interpretations of the left lateral anterior activation of the hippocampus by both face-face and face-laugh encoding in our study. First, it could indicate that encoding of such non-verbal associative information normally involves contributions from both the left and right hippocampus. Although the left hippocampus has been consistently associated with verbal memory (see; Davachi, 2006; Lee, Yip, & Jones-Gotman, 2002, for reviews of patient and imaging studies, respectively), others have argued that lateralization of function to the left and right hippocampus is not accurately explained by material specificity (see Jones-Gotman et al., 1997; Kennepohl et al., 2007). However, the extent to which non-verbal tasks are purely non-verbal has been questioned (see Lee et al., 2002). We cannot, therefore, rule out the alternative interpretation that, despite selecting stimuli and stimulus-stimulus associations that were very difficult to verbalize, participants nevertheless attempted to encode the study material verbally, leading to left hippocampal activation.

5.6. Other brain regions

Extensive areas of occipital, parietal, temporal and frontal cortex were activated during study and recognition of face-face and face-laugh paired associates. As expected, study and recognition of face-face paired associates produced greater activation in the ventral visual-processing stream than study and recognition of face-laugh paired associates. This included activation of occipital cortex and inferior temporal, fusiform and parahippocampal gyri, reflecting the greater visual-processing demands of the face-face than the face-laugh task. In contrast, study and recognition of face-laugh paired associates produced greater activation than study and recognition of face-face paired associates in auditory cortex (superior temporal and transverse gyri) and other regions involved in auditory processing, sound, such as the inferior parietal gyrus and inferior frontal gyrus (Poremba & Mishkin, 2007). The middle temporal gyrus was also activated more by study and recognition of face-laugh than face-face pairs.

Another interesting difference between our two types of material was found in the insula response. Activation of the insula was greater during study and recognition of face-laugh than face-face paired associates. Previous work has shown that the insula is activated more by cross-modal matching of objects than by matching objects presented within the same modality (Banati, Goerres, Tjoa, Aggleton, & Grasby, 2000; Hadjikhani & Roland, 1998). It has, therefore, been argued that the insula acts as a mediating region that enables exchange of information between unimodal regions (Amedi, von Kriegstein, van Atteveldt, Beauchamp, & Naumer, 2005). Greater activation of this region during study and recognition of our face-laugh than our face-face paired associates is consistent with this view. Our data may therefore suggest that the insula is not only activated during cross-modal perceptual processing of objects, but also when previously unrelated information from different modalities has to be combined and the associations retrieved from memory. Alternatively, our insula activation may reflect perceptual processing of the laughs. The insula has been shown to be activated by the auditory presentation of laughter, both when participants are required to self-induce the corresponding emotion while they listen and when they are required to detect artificial pitch-shifts (Sander & Scheich, 2001, 2005; Sander et al., 2003). This region is also activated in a similar way by other sounds that are emotionally meaningful, such as crying (Sander & Scheich, 2001, 2005; Sander et al., 2003). Listening to laughing and crying in these studies was also found to activate the amygdala (Sander & Scheich, 2001, 2005; Sander et al., 2003). We did not, however, find a difference in activation of the amygdala between study and recognition of face-laugh and face-face paired associates; the amygdala was activated by both tasks during the study phase, but no significant activation in this structure was observed during the recognition phase.

Activation of the frontal cortex was extensive during study and recognition of both types of stimulus material, and, of particular note, there was no strong evidence of any difference in the lateralization of frontal-lobe activation between the study and recognition phases. The hemispheric encoding/retrieval asymmetry (HERA) model (Nyberg et al., 1996; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994) holds that the left prefrontal cortex is activated by encoding and the right prefrontal cortex is activated by retrieval. In our study, however, we found no evidence for lateralization of encoding and retrieval to left and right prefrontal cortex, respectively. We found significant bilateral activation in the middle and superior frontal gyri and activation in the left precentral gyrus during both study and recognition. The only differences observed were in the medial and inferior frontal gyri. The medial frontal gyrus was activated during recognition but not study. Inferior frontal activation was left-lateralized during study but bilateral during recognition (see Tables 4 and 6).

Finally, we observed bilateral activation of the thalamus and anterior and posterior cingulate gyrus during recognition of face-face and face-laugh paired-associates (see Table 6). Activation in these regions was expected because both the thalamus and cingulate cortex are thought to contribute to the brain systems mediating memory (Aggleton & Brown, 1999). Activation of posterior cingulate gyrus has been observed during recognition in a number of previous imaging studies. In the case of word recognition, activation of this region has been found to be associated specifically with recollection (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Wheeler & Buckner, 2004; Yonelinas et al., 2005), whereas for non-verbal stimuli, it has been recently shown to be activated by both recollection and high levels of familiarity (Montaldi, Spencer, Roberts, & Mayes, 2006).

6. Conclusion

We found that the hippocampus was activated to a similar extent by the intentional study of face-face and face-laugh paired associates. This finding suggests that the hippocampus is involved in encoding both types of stimulus association. We also found no difference in hippocampal activity between our two types of stimuli during the recognition phase, although the hippocampus was not activated by these conditions, relative to our baselines. We therefore found no evidence that the hippocampus was engaged to a different extent during recognition tests for same-type (face-face) and different-type (face-laugh) item associations.

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