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Medial prefrontal–hippocampal connectivity during emotional memory encoding predicts individual differences in the loss of associative memory specificity

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ABSTRACT

Emotionally charged items are often remembered better, whereas a paradoxical loss of specificity is found for associative emotional information (specific memory). The balance between specific and generalized emotional memories appears to show large individual differences, potentially related to differences in (the risk for) affective disorders that are characterized by 'overgeneralized' emotional memories. Here, we investigate the neural underpinnings of individual differences in emotional associative memory. A large group of healthy male participants were scanned while encoding associations of face-photographs and written occupational identities that were of either neutral ('driver') or negative ('murderer') valence. Subsequently, memory was tested by prompting participants to retrieve the occupational identities corresponding to each face. Whereas in both valence categories a similar amount of faces was labeled correctly with 'neutral' and 'negative' identities, (gist memory), specific associations were found to be less accurately remembered when the occupational identity was negative compared to neutral (specific memory). This pattern of results suggests reduced memory specificity for associations containing a negatively valenced component. The encoding of these negative associations was paired with a selective increase in medial prefrontal cortex activity and medial prefrontal–hippocampal connectivity. Individual differences in valence-specific neural connectivity were predictive of valence-specific reduction of memory specificity. The relationship between loss of emotional memory specificity and medial prefrontal–hippocampal connectivity is in line with the hypothesized role of a medial prefrontal–hippocampal circuit in regulating memory specificity, and warrants further investigations in individuals displaying 'overgeneralized' emotional memories.

1. Introduction

Emotional events can be pervasively engrained in memory, as demonstrated by vivid recollections of flashbulb-memories (Brown & Kulik, 1977) or intrusive memories of patients with post-traumatic stress disorder (Brewin, Gregory, Lipton, & Burgess, 2010). Indeed, an emotional enhancement effect is reliably found experimentally when probing memory for items like faces, objects, scenes, words or movie clips that are charged with a negative emotional valence compared to neutral items (Bradley, Greenwald, Petry, & Lang, 1992; Cahill & McGaugh, 1995; Cahill et al., 1996; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000; Hamann, Ely, Grafton, & Kilts, 1999; Talmi & Moscovitch, 2004). However, a somewhat different picture emerges when memory is tested beyond isolated items, probing memory for associated items or spatiotemporal context. While memory for negative items themselves is enhanced compared to neutral items, memory for associated items or associated context is impaired (Bisby & Burgess, 2014). Even when an impaired memory for associative detail is found, the subjective sense of vivid recollection can be increased (Rimmele, Davachi, Petrov, Dougal, & Phelps, 2011).

The paradoxical modulatory effect of emotion on memory is reminiscent of the so-called 'weapon-focus' effect reported in the eye-witness literature, whereby a perceived item of negative valence (such as a weapon) impairs witnesses' ability to identify the perpetrator carrying the gun (peripheral associated information) (Christianson & Loftus, 1991; Migueles & Garcia-Bajos, 1999; Steblay, 1992). It has thus been argued that emotional valence might enhance the likelihood that the theme or gist of an event is remembered at the expense of memory for specific details (Adolphs, Tranel, & Buchanan, 2005). Recently, it has been

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postulated that emotionally arousing items attract particular attention, thereby enhancing binding of its constituting elements. At the same time, the association of the central object with contextual information and other objects is weakened (Mather, 2007). These two tenets are not contradictory, but are rather shown to complement each other in explaining the emotional memory paradox. When comparing encoding of negative versus neutral material, detailed memory is preserved for particularly those objects that are central, whereas memory for the non-emotional background becomes less detailed (Kensinger, Garoff-Eaton, & Schacter, 2007). Similarly, when encoding emotional material, the increased subjective sense of recollection is found to be related to an enhanced memory for the what, where and when of a specific emotional item, whereas peripheral details and associations to other items occurring at the same time are poorly remembered (Bisby & Burgess, 2014; Rimmele, Davachi, & Phelps, 2012; Rimmele et al., 2011). While an emotionally arousing picture impairs memory for the background pattern, it does not impair item recall, item recognition, or location memory of another central picture or object and its features (Erk et al., 2003; Mather, Gorlick, & Nesmith, 2009; Touryan, Marian, & Shimamura, 2007). Emotional items also impair memory for the specific association among them. For instance, one study found that recognition memory for negative word-pairs was found to be impaired compared to neutral or positive word pairs, and this was expressed primarily as an increased false alarm rate for re-arranged negative word pairs (Pierce & Kensinger, 2011). Notably, the hit rate for negative words demonstrated decreased forgetting across the one week consolidation period, but this finding was paralleled by a similar increase in the false alarm rate. Thus, while the emotional valence boosts item recall and item recognition, it reduces memory specificity for associations and background context.

When investigating the brain basis of the emotional modulation of memory, a distinction is thus warranted between memory for the central item and memory for associated information and spatiotemporal context. Corroborating this distinction is the finding that damage to the amygdala, a brain region deemed to be essential for emotional modulation of memory (McGaugh, 2004; Phelps, 2004), impairs gist memory while retrieval of associated detail is preserved (Adolphs et al., 2005). Individual differences in emotion-modulated item memory can be related at the neural level with activity in the amygdala and other medial temporal lobe (MTL) regions, as well as their mutual connectivity (Dolcos, LaBar, & Cabeza, 2004; Hamann et al., 1999; Kilpatrick & Cahill, 2003; Murty, Ritchey, Adcock, & LaBar, 2010; Ritchey, Dolcos, & Cabeza, 2008). The neural mechanisms underlying the emotional regulation of memory specificity are, however, less clear. In general, there is a wide set of regions implicated in the retrieval of associative detail in both cued recall and source memory tasks, including the medial prefrontal cortex (mPFC), posterior midline, bilateral parietal and medial temporal regions (Hayama, Vilberg, & Rugg, 2012; Vilberg & Rugg, 2014). Particularly, the mPFC has been found to respond also to emotional valence and arousal (Geday, Gjedde, Boldsen, & Kupers, 2003; Geday, Kupers, & Gjedde, 2007; Phan et al., 2003), to social and self-referential processing (Gusnard, Akbudak, Shulman, & Raichle, 2001; Mitchell, Banaji, & Macrae, 2005; Mitchell, Neil Macrae, & Banaji, 2005) and emotion regulation (Banks, Eddy, Angstadt, Nathan, & Phan, 2007; Quirk & Beer, 2006). Connectivity between the mPFC and amygdala have been found to be important for regulating emotions (Banks et al., 2007; Quirk & Beer, 2006). Recent findings have converged in implicating the mPFC also in the integration of information in pre-existing knowledge structures, so-called schemas that appear to be memories generalized over several episodes (Lewis & Durrant, 2011; Van Kesteren, Ruiter, Fernández, & Henson, 2012). Thus, it can be suggested that the mPFC plays a critical role in assimilating generalized memories that are less specific to an individual episode. A recent study in mice has added critical support for this hypothesis by revealing mPFC–hippocampal connectivity mediates specificity of emotional memories. However, it remains to be tested whether this interaction is also involved in regulating emotional associative memory in humans. Interestingly, a recent study in mice revealed that specific thalamic nuclei regulate the specificity of emotional memories by modulating mPFC–hippocampal connectivity (Xu & Südhof, 2013). Thus, connectivity between mPFC and hippocampus appears critical in regulating emotional associative memory specificity, but this remains to be tested in humans.

Here, we investigate the neural mechanisms related to the modulation of associative memory specificity by emotional item valence. Individual differences in neural mechanisms might be particularly interesting when informing future research into extreme impairments in emotional memory specificity found in clinical populations (Foa, Gilboa-Schechtman, Amir, & Freshman, 2000; Moradi, Taghavi, Neshat-Doost, Yule, & Dalgleish, 2000; Watkins, Vache, Verney, & Mathews, 1996). We explore these individual differences here in a normal population using a memory encoding task where faces need to be associated with occupational identities. This task has been frequently used in the literature to elucidate individual variation in associative memory (Dominique & Papassotiropoulos, 2006; Erk et al., 2010, 2011; Werner et al., 2009). Here, we added a manipulation of emotional valence of the occupational identity labels to allow us to look at individual differences in emotional associative memory. Specifically, a large group of young healthy men were scanned while encoding associations of individual faces and either neutral (e.g., 'driver') or negative (e.g., 'murderer') occupations, and were asked later to identify the particular neutral and negative occupational identity associated with each particular face. Broadly, this laboratory task resembles a line-up situation where a victim needs to identify a villain from a range of other identities. Memory performance is operationalized on a general, gist-level (a face is associated with an occupational identity from the correct valence-category but not the exact occupational identity) and a specific, detailed level (the specific face–occupational identity association is remembered correctly). A loss of memory specificity can be expected for those associations that consist of negative occupational identities, potentially mediated by interactions of MTL regions with the mPFC.

2. Materials and methods

2.1. Participants

One-hundred-twenty young healthy male volunteers in the age range of 18–31 (mean age 21.9; SD = 2.63) provided informed consent to participate in the study. All subjects were right-handed and pre-screened to exclude a history or current status of psychiatric, neurological or endocrine disorder, and to exclude the consumption of illicit drugs or medications affecting the central nervous or endocrine systems at any point over the past six months. The study was conducted in accordance with guidelines of the local ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen, The Netherlands) and the declaration of Helsinki. To ensure that all subjects in the final sample understood and performed the task correctly, we removed those participants from further analysis that performed extremely poorly. The threshold was set at two items correct, where the items were counted correct when both valence + identity was correct. Two items corresponds to the number of items that can be expected to be guessed correctly if subjects were fully aware of the valence of each face and completed every item of the test (32 faces, 16 negative

occupations, 16 neutral faces, 1/16 chance of having the occupation correct per item, 32 ∗ 1/16 = two items). Using this threshold resulted in a final sample of 102 participants for further analysis.

2.2. Procedure

The experiment was embedded in a larger study that entailed two visits of each participant, separated by on average two weeks (minimum of five days). Here, we focus on data from one task, while controlling for order-effects.

2.3. Experimental paradigm

Participants performed the emotional face–occupation association task inside the MRI scanner, where they were presented simultaneously with pictures of faces and written words describing occupations that were either of neutral (e.g. driver) or of negative valence (e.g. murderer). To encourage the subjects to engage in deep encoding, the instruction during the associative learning of the face–occupation pairs was to imagine the person in the picture matching the description underneath the photo. Participants then indicated with a button press whether they could imagine the person being labeled with the associated description. Furthermore, they were instructed to remember these associations for a subsequent memory test.

Thirty-two pairs were used per subject. Half of these pairs included an occupational identity word that was of neutral valence, whereas the other half included a negative occupational identity word. The unique combinations of these 32 faces and 32 occupational identities were counterbalanced across subjects. The words in the negative and neutral categories were matched in terms of word length and frequency, but differed in terms of rated valence and arousal as shown by independent behavioral pilots. Furthermore, the two sets of words did not differ significantly in terms of their semantic similarity (see Table 1).

The pairs were presented in study blocks of 24 s, during which four pairs were presented for 6 s each. There were four blocks of face–occupation associations with a neutral valence, and four blocks that included negative occupational identity words. The experiment included also three blocks of a perceptual control task, where participants were presented with three blocks of four trials, each requesting a perceptual judgment. Here, subjects were presented with head contours (gray silhouettes against a colorful background), and had to indicate with a button press whether the left or right ear was lower in the picture. The sequence of blocks was counterbalanced across subjects, and blocks of the three conditions were presented in alternating order such that each block was always followed by a block from a different condition. Each block was separated by a 2 s interval, during which participants were cued with the task of the ensuing block (either "associate face" was presented for encoding blocks or "distance ear" for perceptual blocks). All blocks were presented in a single scanner run.

After a delay period, participants were tested outside the scanner on their memory for the associations. While there was variance between subjects in the delay between encoding and recall due to practical reasons (mean: 47:31 mins, SD = 09:44 mins, range: 11:40–1:00:53), the delay period did not significantly predict individual subject performance on behavioral memory measures reported here. Furthermore, given that we recorded the delay for each subject, we insured it would not bias the reported brain–behavior correlation by taking it into account as a control variable in a partial correlation analysis. At test, subjects were given lists of both the face-pictures and written occupational identities that were presented at encoding, and were asked to recall the associations and write the identities underneath the faces (cued recall task). They were not given any novel faces or occupational identities as lures. Furthermore, subjects were instructed to avoid guessing and to respond with those associations that they recalled with confidence (see Fig. 1).

Table 1
Characteristics of neutral and negative words.

Word characteristic	Mean neutral	Mean negative	*P*-value
Length	8.88	8.34	0.26
Frequency	111.81	91.69	0.53
Valence	5.38	2.82	<0.001*
Arousal	2.26	4.41	<0.001*
Semantic similarity	0.30	0.28	0.09

Word characteristics were compared for neutral and negative word lists. The word length was determined by the number of letters contained in the word. The frequency of these words in the Dutch language were obtained from the Celex-database (Baayen, Piepenbrock, & Rijn, 1993). The ratings of valence and arousal of each word were obtained by an independent behavioral pilot in a separate group of 18 subjects ($N = 18$). The valence of each word was rated on a scale from 1 to 9 where a lower score equals higher emotional valence, whereas the evoked arousal of each word was rated on a scale from 1 to 9 were a higher score equals higher arousal. Corpus-based pairwise word similarity measures were obtained from Cornetto, a lexical-semantic database for the Dutch language (Vossen et al., 2013). Semantic similarity was calculated using Lin's information-theoretic measure of similarity (Lin, 1998), resulting in word-unique values ranging from zero (completely unrelated) to one (identical).

2.4. Behavioral analysis

Behavioral measures were analyzed in IBM SPSS Statistics 21. Behavioral performance on the cued recall task was scored by categorizing items into four bins based on response accuracy. Besides the 'misses' (items where no response was given), the responses could be divided into those that have both an incorrect occupational identity and an incorrect valence ('incorrects'), those that have an incorrect occupational identity yet belong to the correct valence ('valence-only correct') and those that have a correct occupational identity ('valence + identity correct'). A measure of memory specificity was then calculated for neutral and negative valence categories separately by dividing the 'valence + identity correct' items by the total 'valence-correct' items (the latter also including the valence-only correct items). The difference between memory specificity scores for each valence was calculated to assess whether the negative valence would lead to the predicted loss of specificity. Subsequently, Student's t tests were performed to determine differences in performance between the negative and neutral valence conditions (paired-sample t test). For all tests α was set at 0.05.

2.5. MR data acquisition

Participants were scanned using a 1.5 Tesla Magnetom Avanto MR-scanner (Siemens, Erlangen, Germany) equipped with a 32-channel phased array head coil (MRI Devices). For blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI) images, we used a $T2^*$-weighted gradient echo planar imaging sequence to collect a series of 128 images during the task run with the following parameters: repetition time (TR): 2.34 s, echo time (TE): 35 ms, 32 oblique transverse slices, flip angle: 90°, slice matrix size = 64 × 64; slice thickness = 3.5 mm; slice gap = 0.35 mm; and field of view (FOV) = 212 × 212 mm^2, and voxel size: 3.3 × 3.3 × 3.5 mm. To ensure reaching a steady-state condition, the first five scans were discarded. Additionally, 3D magnetization-prepared rapid gradient echo (MPRAGE) anatomical T1-weigthed images were acquired for normalization purposes (176 slices, 1.0 mm isotropic resolution, TR = 2730 ms, TE = 2.95 ms).

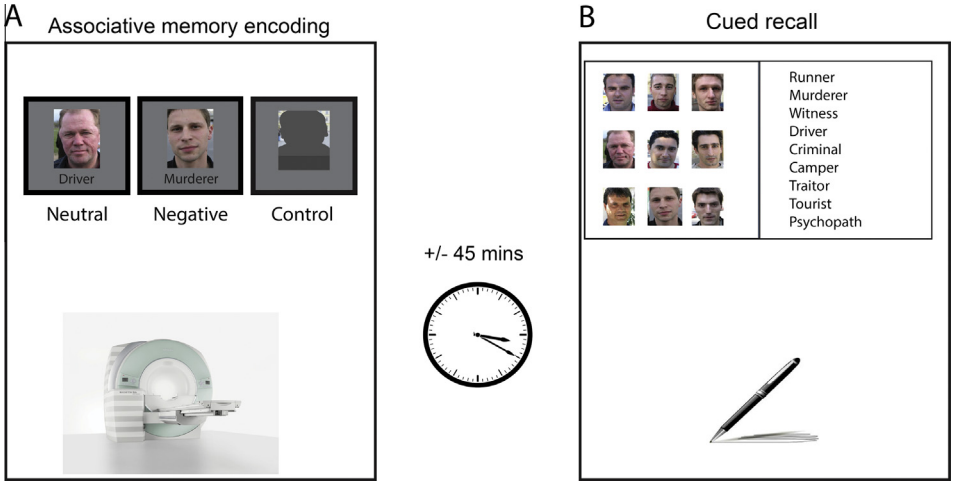

Fig. 1. Task setup. The task consisted of two phases, namely an associative memory encoding phase, and a cued recall phase. (A) In the associative memory encoding phase, participants were presented in the scanner with pictures of faces paired with a written identity (in Dutch, but English translations shown here), divided into blocks of identities with a neutral valence, and identities with a negative valence. Participants indicated with a button press whether they could imagine the written identity belonging to the face in the picture. In the control task blocks, participants were presented with a gray head silhouette, and responded with a button press whether the left or right ear was lower in the picture. (B) In the cued recall phase, participants were presented with a list of all face pictures and a list containing all written identities (subsets are shown here). Participants had to recollect the original face-identity pairs by writing the identity underneath the corresponding picture.

2.6. MR data analysis

Functional MRI data were analyzed using SPM8 (UCL, London: http://www.fil.ion.ucl.ac.uk/spm), following standard preprocessing procedures. Specifically, images were corrected for slice-timing and realigned to account for three-dimensional motion. After co-registration of the structural and the functional images, all functional images were normalized into standard stereotactic space using the T1 (Montreal Neurological Institute [MNI] 152-template). Smoothing was performed with a Gaussian kernel of 8 mm full-width at half-maximum.

Next, single subject general linear models were constructed with 24-s boxcar regressors modeling task blocks separately for neutral valence, negative valence and control task. Regressors were temporally convolved with the canonical hemodynamic response function of SPM8. The six movement parameters were included as covariates to model potential movement artifacts. Contrast parameter images were generated at the single subject level for negative and neutral encoding versus the perceptual control task. These individual parameter estimate maps were statistically scrutinized at the second level. In a factorial ANOVA emotion type was added as within-subject factor and session order (whether the session was the first or the second session) as between-subject factor.

Effective connectivity between regions was determined using psycho-physiological interactions (PPIs) as implemented in SPM8. PPI-analyses assess differences in co-activation of a seed region (physiological factor) with the rest of the brain as modulated by an external factor (psychological factor). Specifically, we examined task-related functional connectivity changes underlying the differential encoding of associations with a neutral versus negative valence. The single-subject GLMs for these analyses included the general de-convolved signal extracted from the seed region, the neutral-negative task-vector and the interaction term, in addition to the six movement parameters defined earlier. The subject-specific parameter estimate for the interaction term was used as input for second-level random-effects analysis. The seed-region was defined by the mPFC activation cluster found in the negative > neutral encoding contrasts, thresholded at $p < 0.001$ uncorrected.

Statistical parametric maps were thresholded and visualized by superimposing T-contrast images onto the standard MNI-image implemented in MRIcron. Connectivity and activity were considered significant using a criterion of $p < 0.05$ Family-Wise Error cluster-corrected for the whole brain (as implemented in SPM8) after an initial voxel-level threshold of $p < 0.001$ uncorrected. Additionally, the hippocampus and amygdala were treated as regions of interest, based on their *a priori* hypothesized roles in associative memory encoding and emotional processing. Statistical inference tests about BOLD-responses in the hippocampus and amygdala were corrected for multiple comparisons in a reduced search region, defined using anatomical masks from the WFU PickAtlas Tool (version 2.4) implemented in SPM.

2.7. Across-subject correlation

To explore brain–behavior associations across participants, PPI measures were extracted from SPM and analyzed using SPSS. A two-tailed simple Pearson correlation and a partial Pearson correlation test controlling for test delay was performed to test the linear relation between PPI-measures on the one hand and valence-related changes in specificity on the other hand. Alpha was set at 0.05 throughout.

3. Results

3.1. Behavioral results

Subjects showed significant memory for the specific face–occupation associations (proportion correct: mean = 0.29, SD = 0.17 versus the chance level of 0.06, $t_{(101)} = 17.07$, $p < 0.001$). Memory for specific face–occupation associations was modulated by valence. Associations with negative occupational identities were less well remembered than associations with neutral occupations, indicating impaired memory for specific associations when emotionally negative (neutral correct: mean = 0.33, SD = 0.20; negative correct: mean = 0.26, SD = 0.17; difference $t_{(101)} = 4.40$, $p < 0.001$). If subjects were unable to remember the specific face–occupation associations correctly, they more often selected an occupation from the same valence category than from the other (correct valence category: mean = 0.13, SD = 0.11; valence category incorrect: mean = 0.09, SD = 0.09, difference $t_{(101)} = 4.40$, $p < 0.001$). This

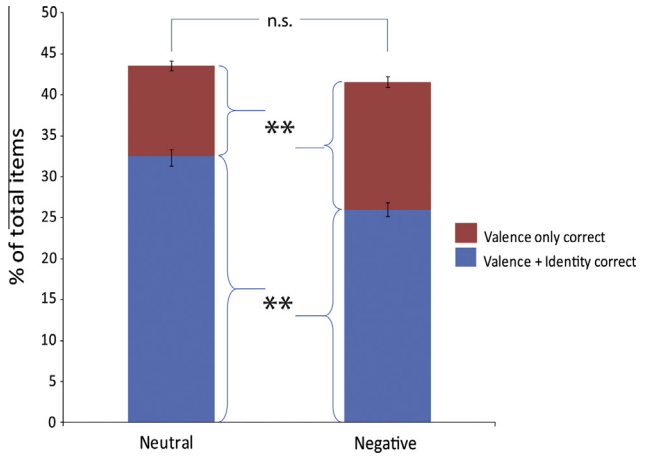

Fig. 2. Behavioral results. The bar graph displays memory performance as proportion of total associations correctly recalled for neutral respectively negatively encoded face–occupation associations. No difference is noticeable with regards to proportion of valence-correct responses for negative and neutral associations (blue + red bars combined). A marked difference between memory recall of neutral and negative associations appears when distinguishing the proportion of those valence-correct responses where identity is also correct (blue bars) versus the proportion of valence-correct responses where identity is incorrect (red bars). Error bars reflect standard error of the mean. n.s.: not significant, $^{**}p < 0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

is indicative of a gist-like, less specific memory of the associated valence-category. This gist-like memory lacking associative specificity was more prevalent for the negatively valenced associations than for neutral ones (negative valence-only correct: mean = 0.15, SD = 0.13; neutral valence-only correct: mean = 0.11, SD = 0.12; difference $t_{(101)} = 4.26$, $p < 0.001$).

Subsequently, we estimated the proportion of trials with correctly remembered face–occupation associations relative to all trials in which at least the valence (the gist) was correct. Here, we observed a shift from specific, associative memory toward a less-specific gist-like memory for negatively valenced occupational identities (see Fig. 2) (memory specificity neutral: mean = 0.73, SD = 0.25; memory specificity negative: mean = 0.63, SD = 0.25; difference $t_{(101)} = 4.01$, $p < 0.001$).

3.2. Imaging results

Compared to the perceptual control condition, encoding of face–occupation associations activated a set of brain regions encompassing ventral visual regions, the MTL and midline structures such as the mPFC, posterior cingulate cortex and precuneus (see Fig. 3a). Two emotional contrasts were calculated across the face–occupation association conditions. Faces with neutral compared to negative occupational identities led to stronger activity in a large area including the left fusiform and parahippocampal gyrus and extending into the lingual gyrus and precuneus, as well as the left dorsolateral prefrontal cortex, left inferior temporal gyrus, bilateral angular gyrus, posterior cingulate cortex (cluster-level FWE corrected; $p < 0.05$), and the hippocampus bilaterally ($p < 0.05$ SVC corrected; Fig. 3b and Table 2). Conversely, increased activation for faces with negative as opposed to neutral occupations was revealed in a large cluster centering in the rostral mPFC extending into the anterior cingulate cortex (−2, 52, 24, cluster-level FWE corrected $p < 0.05$) (Fig. 3c and Table 3).

Given our hypothesis that the mPFC is part of a network relevant for memory specificity and generalization, we used this mPFC cortex cluster as a seed region for a psycho-physiological interaction analysis (PPI). This enabled us to assess at which brain region is connectivity with the mPFC seed region (physiological factor) modulated by the emotional valence of the occupation (psychological factor). The mPFC displayed a relative increase in functional connectivity during negative associative encoding with a MTL cluster (cluster corrected $p < 0.05$), which includes both the right hippocampus (SVC-corrected $p < 0.05$) and amygdala (SVC-corrected $p = 0.002$) (Fig. 4a and Table 4). A second cluster was detected in the left inferior occipital gyrus (cluster corrected $p < 0.05$). The encoding of negative associations is thus found to be associated with a relative increase in functional connectivity between the mPFC and the MTL and early visual processing areas.

To probe the behavioral relevance of this differential connectivity, we tested whether the valence effect on medial prefrontal–medial temporal connectivity was associated with individual differences in memory specificity. Functional connectivity between the mPFC and right hippocampus for the contrast negative versus neutral occupations correlated positively ($r_{(101)} = 0.224$, $p = 0.024$ two-tailed) with the valence related differences in memory specificity (negative memory specificity – neutral memory specificity) after removing a potent bivariate outlier (Cook's Distance > 0.25). We did not find a reliable correlation for the right amygdala ($r_{(101)} = 0.068$, $p = 0.500$ two-tailed) or the early visual cortex ($r_{(101)} = 0.141$, $p = 0.161$ two-tailed). When taking a partial correlation, controlling for time delay, the correlation remains significant ($r_{(101)} = 0.219$, $p = 0.029$ two-tailed).

4. Discussion

The current results build on previous literature by demonstrating a loss of memory specificity for associative information charged with a negative emotional valence. Particularly, we demonstrate that, despite an overall preserved gist memory (preserved memory for the valence of occupational identity associated with a face), there is a loss of memory specificity evidenced by impaired retrieval of the specific associated occupational identities for the negative valence category. When encoding negative associations, a selective increase in activation is observed in the mPFC along with reduced activity in, among others, the bilateral hippocampus, compared to encoding neutral associations. Furthermore, we find an increase in connectivity between the mPFC and right hippocampus and amygdala during negatively valenced encoding. The behavioral relevance of this valence-specific interplay between hippocampus and mPFC is further evidenced by a negative correlation with memory specificity in an across-subject analysis. While this finding is correlational and thereby does not confirm causality, this suggests that individual differences in medial-prefrontal–hippocampal coupling may have an impact on an individual's memory specificity in an emotional context.

The behavioral finding of an emotion-induced loss of associative memory specificity is in line with both laboratory studies (Bisby & Burgess, 2014; Rimmele et al., 2011, 2012), and observations from the eyewitness literature (Christianson & Loftus, 1991; Migueles & Garcia-Bajos, 1999; Steblay, 1992) that report impairments in the recall of associated detail. The apparent paradox in the literature between an emotional enhancement effect for the recall and recognition of items, and an emotional impairment effect for retrieving associations and peripheral details can be reconciled when distinguishing between gist (general) and detailed (specific memory). The emotional enhancement effect of gist memory has been shown to be mediated by the modulatory influence of the amygdala on the MTL (Kilpatrick & Cahill, 2003; LaBar & Cabeza, 2006; McGaugh, 2004). Studies in rats have shown that the amygdala is important for gist memory, but not detailed recollection (Farovik, Place, Miller, & Eichenbaum, 2011). This relatively selective role of the amygdala in gist memory is corroborated by studies of patients

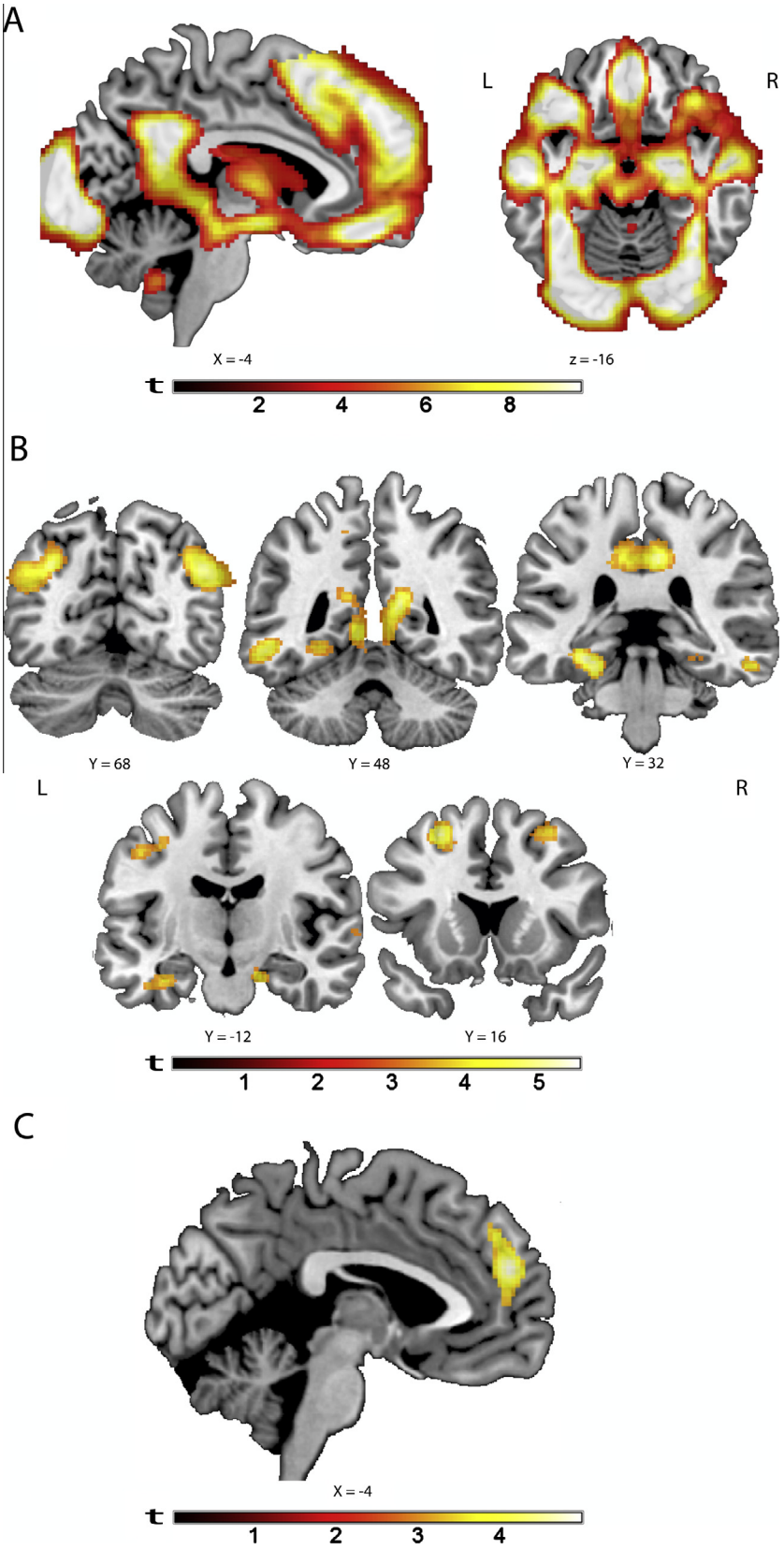

Fig. 3. Main activation effects of encoding faces associated with occupational identity words (images displayed at a threshold of $p = 0.001$ uncorrected, cluster size threshold: 30 voxels). (A) Contrast of encoding (negative + neutral) versus the sensorimotor control task. (B) Contrast of encoding neutral associations versus negative associations. (C) Contrast of encoding negative versus neutral associations.

Table 2
fMRI results encoding neutral > negative.

Brain region	Cluster size (voxels)	Cluster *P*	*T*-value	Local maxima		
				x	*y*	*z*
L fusiform/parahippocampal gyrus bilateral precuneus	1882	<0.001	5.55	−32	−38	−12
L middle frontal gyrus	468	0.003	5.55	−24	12	54
L middle occipital gyrus/L angular gyrus	813	<0.001	5.05	−34	−72	34
Bilateral posterior cingulate gyrus	859	<0.001	5.04	8	−34	38
R middle occipital gyrus/R angular gyrus	990	<0.001	4.86	46	−70	32
L inferior temporal gyrus	275	0.038	4.61	−56	−48	−10
L white matter	356	0.013	4.46	−24	−18	46
SVC L hippocampus	308	<0.001	5.51	−30	−36	−12
SVC R hippocampus	134	0.006	4.21	34	−38	−8

Clusters of voxels where activity is higher during the encoding of neutral versus negative face-identity associations. For each cluster, the local maximum is reported. Cluster *p*-value is whole brain corrected at the cluster level (FWE, $p < 0.05$), or small-volume corrected (SVC) for an anatomical mask based on the AAL-atlas. All coordinates are in MNI space. L = left, R = right.

Table 3
fMRI results encoding negative > neutral.

Brain region	Cluster size (voxels)	Cluster *P*	*T*-value	Local maxima		
				x	*y*	*z*
Medial prefrontal cortex	573	0.001	4.99	−2	52	24

Clusters of voxels where activity is higher during the encoding of negative versus neutral face-identity associations. For each cluster, the local maximum is reported. Cluster *p*-value is whole brain corrected at the cluster level (FWE, $p < 0.05$). All coordinates are in MNI space. L = left, R = right.

with selective amygdala lesions that revealed a relative impairment of retrieving central gist-based elements, but not peripheral details of complex stimuli (Adolphs et al., 2005). However, the neural mechanism underlying the emotional impairment of specific detailed memory has not been sufficiently investigated yet in the context of emotional memory.

The current results suggest that interactions between the mPFC and the hippocampus may play a critical role in driving inter-individual differences in memory specificity. These results converge with recent rodent work that demonstrated the role of a circuit including the mPFC, thalamic nucleus reuniens and hippocampus in regulating the specificity of the encoding of fear memories (Xu & Südhof, 2013). On the one hand, increased activation of bilateral hippocampal and parahippocampal regions during encoding of the more specifically remembered neutral associations suggests that MTL activity is beneficial for memory specificity. On the other hand, increased mPFC connectivity with the right MTL during encoding of negative associations might indicate that the mPFC regulates memory specificity by altering encoding activity in the MTL. Based on rodent work, it could be speculated that the mPFC connects via the nucleus reuniens to inhibitory interneurons in the hippocampus (Dolleman-Van der Weel, Lopes da Silva, & Witter, 1997), effectively causing a downregulation of hippocampal processing during negative encoding and resulting in increased activity in the neutral condition. Moreover, and potentially in line with this interpretation, the activity and connectivity contrasts revealed different parts of the MTL. On the one hand, the mPFC seems to show an interaction with an anterior part of the right MTL including the amygdala and anterior aspects of the hippocampus. On the other hand, the main effects of neutral versus negative encoding were found in more posterior regions of the hippocampus and the parahippocampal gyrus. The anterior region of the hippocampus might be particularly suited for processing more general gist-based information (Gutchess & Schacter, 2012), whereas more posterior regions might be more specialized to processing detailed information specific to an episode (Poppenk & Moscovitch, 2011). This is supported by recent investigations of

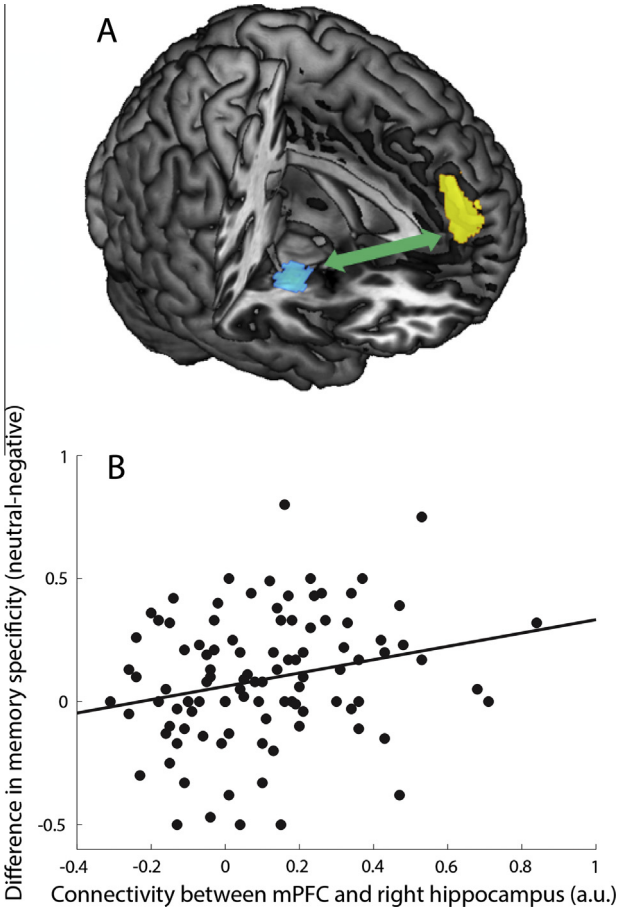

Fig. 4. MPFC–hippocampal connectivity. (A) Psychophysiological analysis with mPFC as seed region (cluster displayed in warm colors) showed a significant coactivation with the right hippocampus and amygdala (cluster displayed in cold colors), as well as the left early visual cortex (not displayed). (B) The PPI-values for connectivity between the mPFC and the right hippocampus (red arrow) are extracted for across-subject correlation. A correlation between mPFC–hippocampus coupling and a loss of memory specificity for negatively valenced associations was found. The more connectivity during encoding of negatively valenced associations relative to neutral valence associations, the more the associated loss of memory specificity in the subsequent memory test ($r_{(102)} = 0.224$, $p = 0.024$). a.u.: = arbitrary units. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

hippocampal activations along the posterior–anterior axis showing that its most anterior aspect is particularly involved in encoding associative information at a coarser, global spatiotemporal scale, whereas the middle and posterior hippocampus are particularly

Table 4
fMRI results PPI-analysis negative > neutral (mPFC-seed).

Brain region	Cluster size (voxels)	Cluster *P*	*T*-value	Local maxima		
				x	*y*	*z*
R hippocampus/amygdala	176	0.039	4.91	28	−10	−12
SVC R hippocampus	43	0.033	4.59	26	−12	−12
SVC R amygdala	110	0.002	4.91	28	−10	−12
L inferior occipital gyrus	323	0.002	3.97	−24	−88	−10

Clusters of voxels displaying increased connectivity with the mPFC-seed during encoding of negative face-identity associations. For each cluster, the cluster local maximum is reported. Cluster *p*-value is whole brain corrected at the cluster level (FWE, $p < 0.05$), or small-volume corrected (SVC) for an anatomical mask based on the AAL-atlas. All coordinates are in MNI space. L = left, R = right.

involved in encoding associative information specific to a particular episode (Collin, Milivojevic, & Doeller, 2015; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013; Poppenk & Moscovitch, 2011). One of the mechanisms by which the connected circuit of the mPFC and hippocampus could regulate associative memory encoding is by shifting between gist and specific encoding. However, as gist-based memory was not directly measured here, future studies should look into this mechanism in more detail.

The mPFC might regulate associative memory encoding by regions in the MTL. A recent model from our group proposes that the mPFC modulates encoding resources in mnemonic regions like the hippocampus in order to maximize efficiency of memory encoding. Particularly, when new incoming information is congruent with prior knowledge only those congruent, abstract features are extracted, integrated and consolidated in a mnemonic trace (Van Kesteren, Rijpkema, Ruiter, Morris, & Fernández, 2014; Van Kesteren et al., 2013). This role of the mPFC and its connectivity with the hippocampus in optimizing the efficiency of hippocampal encoding can be extended to the current results. The mPFC could be interpreted to shift encoding resources to the central item features (e.g. a gun) that are necessary for survival, at the expense of peripheral, detailed features (e.g., print of the t-shirt that the shooter was wearing). While the current data does not allow making inferences on causality, they converge with previous literature showing that both the amygdala and mPFC can modulate specificity of associative memory encoding. In the context of the present study it could thus be speculated that the mPFC regulates hippocampal-based associative memory processes. However, the reverse direction is also fathomable, namely that emotional valence causes the amygdala to bias the hippocampus to shift to a gist-based encoding mode that also recruits the mPFC. Further studies should elucidate the directionality of the shift with emotional valence to less specific encoding of emotional memories.

The suggested mechanism might serve to enhance encoding efficiency such that the central gist features are encoded particularly well. The net result of this process would be a shift in focus of encoding to central gist features at the expense of peripheral associated information or less relevant detail. Future studies should measure both associative memory and recognition and recall of singular items (faces and occupational identity words) and relate these processes separately to their neural correlates. An enhanced storage of central gist features that are emotionally salient is evolutionary valuable in predicting potential threats in the future that are globally similar to the initial experience. The loss of specificity for remembering associated detail seems less advantageous for survival. However, a shift from high specificity to higher sensitivity has potential survival value. In adverse situations it is adaptive to minimize the risk for false negatives in the detection of potential threats (Van Marle, Hermans, Qin, & Fernández, 2009). However, it might become manifest maladaptively in affective syndromes characterized by overgeneralization of emotional memories.

The balance between emotional gist memory and specific memory bears special relevance for clinical conditions like PTSD, depression and generalized social phobia. Pronounced emotional preferences of gist memory are reported in these patient groups (Foa et al., 2000; Moradi et al., 2000; Watkins et al., 1996), and they seem to focus on summarizing the gist rather than retrieving detail when recounting autobiographical events (Williams et al., 2007). Emotional flashbulb-memories and intrusive recollections in post-traumatic stress disorder are often vivid, but at the same time lacking quality of contextual detail (Bluck & Li, 2001; Brewin, 2007; Brewin, Huntley, & Whalley, 2012; Ehlers, Hackmann, & Michael, 2004; Neisser & Harsch, 1992; Talarico & Rubin, 2003). The loss of specificity in PTSD could underpin the characteristic phenomenon that seemingly neutral cues in 'safe' environments induce vivid and disturbing recollections (Lissek et al., 2005; Mahan & Ressler, 2012). This and other PTSD-symptoms associated with a loss of memory specificity are found to be related to altered functioning of the mPFC (Shin, Rauch, & Pitman, 2006; Williams et al., 2006). This raises the interesting possibility that overgeneralized fear memories in PTSD could be due to differential modulation of mnemonic representations by the mPFC. Similarly, depression is characterized by overgeneralization and reduced specificity of emotional memories (Dalgleish et al., 2007; Park, Goodyer, & Teasdale, 2002; Watkins & Teasdale, 2001; Watkins et al., 1996; Williams et al., 2007). Depression is also linked to altered functioning of the mPFC, especially its most ventral aspect which is often related to aberrant self-relevant and emotional processing (Lemogne, Delaveau, Freton, Guionnet, & Fossati, 2012). It would be important to investigate the role of medial prefrontal–hippocampal connectivity in emotional associative encoding further, and particularly explore their bearing on individual differences in emotional memories in clinical conditions.

The current paradigm asked participants to study occupational identities paired with faces, which is a social task. From an evolutionary perspective, it may make sense to broadly categorize our peers into negative, neutral or positively labeled peers. This information is necessary to inform hierarchical ranking of peers and guiding our behavior toward them (e.g., avoiding 'negative' peers). However, previous studies have shown that social learning is a unique type of learning that is subserved by the amygdala (Kumaran, Melo, & Duzel, 2012). Future studies employing non-social emotional associative learning paradigms should elucidate whether the neural mechanism alluded to in this paper can be characterized as a domain-general emotional associative memory process rather than a specific type of social learning. Alternative explanations of our results are possible as well. A selective increase in mPFC activation is generally found when processing emotional information, particularly in the more rostral region of the mPFC that was found here (Etkin, Egner, & Kalisch, 2011). It could be that this activation is not specific to memory, but a general response to emotional information. Behaviorally, emotional information could be distracting to such an extent that participants are not directing sufficient attentional resources to encoding. The deficit in memory specificity is then simply due to distraction from the online task at hand. However, this explanation is unlikely as we find no overall difference in gist-based memory performance between the two

valence categories, whereas this would be expected if less attention was paid when encoding negatively valenced associations. Furthermore, the relation of memory specificity to mPFC connectivity with the hippocampus (a region essential for associative memory) also speaks against this alternative interpretation. The reduction of memory specificity for negative associations could alternatively originate from retrieval effects. For instance, negative identities are semantically grouped more closely and are more interfering with each other upon retrieval. Furthermore, it could be that the effect is a consolidation effect (despite the short delay) as negative associative information has been shown to be become less specific across longer delays (Pierce & Kensinger, 2011). However, the relation observed here between memory specificity and activation and functional connectivity during encoding provides novel evidence that such effects can also originate at encoding.

There are some limitations of this study that should be noted. The study employed a blocked design that did not allow for trial-specific characterization of neural activity supporting memory. Indeed, an event-related design would have allowed specific item effects to be discerned for successful and unsuccessful encoding. Here, encoding blocks contained different levels of encoding success, and transient emotional effects are difficult to separate from sustained mood effects. However, to ensure reliable assessments of an individual subjects' response, we leveraged on the increased detection power and design efficiency of a blocked design (Friston, Zarahn, Josephs, Henson, & Dale, 1999; Liu, Frank, Wong, & Buxton, 2001; O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012), as in previous studies of individual differences in memory (Dominique & Papassotiropoulos, 2006; Erk et al., 2010, 2011; Werner et al., 2009). Furthermore, an important additional test would have been to compare familiarity, recognition and recall for the faces and occupational identities in isolation across valence categories. This test might have found a preserved or even enhanced item recognition memory for negative identities as well as the faces associated with negative identities, further supporting a dissociation of gist and specific memory.

A further limitation is that positive emotional valence was not included in the task manipulation. One could speculate that the effect observed here is driven by arousal, not emotional valence per se, and therefore might be equally present for positive emotion. Furthermore, only men were included in the sample. The menstrual cycle has been shown to influence emotional modulation of memory and potential stress and cortisol effects in women (Sakaki & Mather, 2012). Therefore, the sample was kept as homogenous as possible, while still allowing the analysis of individual differences pertaining to emotional memory encoding. Thus, future studies should have a symmetric valence manipulation including positive emotions in a sample that also includes women, perhaps controlling for menstrual cycle.

In summary, we demonstrated an emotional impairment effect on memory specificity of face-identity associations. We found a selective increase in mPFC-activity and mPFC–hippocampal connectivity during encoding of associations with a negative valence versus those with a neutral valence. Furthermore, we show that the loss of specificity of associative memories was related to an increase in mPFC–hippocampal connectivity. This finding is in line with the role of a mPFC–hippocampal circuit regulating memory specificity, and suggests future directions for investigating the role of this circuit in regulating emotional associative memory specificity in individuals with 'overgeneralized' emotional memories.

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