

1                                    **Emotional arousal impairs association-memory:**  
2                                    **Roles of amygdala and hippocampus**

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25       **2 Tables**

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43 **Abstract**

44 Emotional arousal is well-known to enhance memory for individual items or events, whereas it  
45 can impair association memory. The neural mechanism of an association memory impairment by  
46 emotion is not known: In response to emotionally arousing information, amygdala activity may  
47 interfere with hippocampal associative encoding (e.g., via prefrontal cortex). Alternatively,  
48 emotional information may be harder to unitize, resulting in reduced availability of extra-  
49 hippocampal medial temporal lobe support for emotional than neutral association-memory. To  
50 test these opposing hypotheses, we compared neural processes underlying successful and  
51 unsuccessful encoding of emotional and neutral associations. Participants intentionally studied  
52 pairs of neutral and negative pictures (Experiments 1–3). We found reduced association-memory  
53 for negative pictures in all experiments, accompanied by item-memory increases in Experiment  
54 2. High-resolution fMRI (Experiment 3) indicated that reductions in associative encoding of  
55 emotional information are localizable to an area in ventral-lateral amygdala, driven by  
56 attentional/salience effects in the central amygdala. Hippocampal activity was similar during  
57 both pair types, but a left hippocampal cluster related to successful encoding was observed only  
58 for negative pairs. Extra-hippocampal associative memory processes (e.g., unitization) were  
59 more effective for neutral than emotional materials. Our findings suggest that reduced emotional  
60 association memory is accompanied by increases in activity and functional coupling within the  
61 amygdala. This did not disrupt hippocampal association-memory processes, which indeed were  
62 critical for successful emotional association memory formation.

63

64 **Significance Statement**

- 65 1. Association-memory for emotional items is often worse than for neutral items.
- 66 2. This has been proposed to result from the amygdala disrupting hippocampal function.
- 67 3. We found evidence for parallel, not opposing, roles of amygdala and hippocampus.
- 68 4. Forgetting of emotional associations is driven by the amygdala.
- 69 5. But successful encoding of emotional associations continues to engage the hippocampus.

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## 72 **1. Introduction**

73           Emotional arousal enhances memory for individual items or events, a robust and  
74 intensely characterized effect that generalizes across many materials and paradigms (Bradley et  
75 al., 1992; Brown and Kulik, 1977; Cahill and McGaugh, 1998). Effects of emotional arousal on  
76 association-memory are more controversial, including null-effects, increases and decreases  
77 (reviews: Mather, 2007; Mather and Sutherland, 2011; Murray and Kensinger, 2013; Yonelinas  
78 and Ritchey, 2015). Emotional arousal may enhance associative memory when the associated  
79 information can be merged so that it effectively functions like one item, e.g., the font color of a  
80 negative word or an object in placed in a semantically relevant scene (D'Argembeau and Van der  
81 Linden, 2004; Kensinger and Corkin, 2003; Mickley Steinmetz et al., 2016). In this view, the  
82 sometimes-observed enhancement of emotional associative memory may be due to the same  
83 memory-enhancing mechanism that operates on emotional items. However, if to-be-associated  
84 information cannot be easily unitized (Pierce and Kensinger, 2011; Rimmele et al., 2011) and  
85 inter-item associations have to be formed, then emotional arousal often impairs associative  
86 memory (Mather, 2007; Murray and Kensinger, 2013). These opposing but presumably  
87 simultaneous effects of emotional arousal on item-memory and inter-item associations have been  
88 recently demonstrated in the same experiment. Using a verbal associative memory paradigm,  
89 Madan et al. (2012) showed, experimentally and with mathematical modeling, that emotional  
90 arousal enhanced memory for individual emotional items (words) and simultaneously impaired  
91 associative binding between items. These results were confirmed with pairs of pictures instead of  
92 words (Bisby and Burgess, 2014; Bisby et al., 2016).

93           Whereas the neural processes underlying the enhancing effects of emotional arousal on  
94 item memory have been intensely characterized (Dolcos et al., 2012; Murty et al., 2010), the

95 neural substrates of the impairing effect of emotional arousal on associative memory have only  
96 begun to be explored (Berkers et al., 2016; Bisby et al., 2016; Murray and Kensinger, 2014).  
97 Here we adapted Madan et al.'s (2012) paradigm for the use with fMRI, a procedure that had  
98 produced simultaneous item-memory enhancing and association-memory impairing effects of  
99 emotional arousal. Our task was designed to equalize attention within and across pairs by having  
100 the two elements of the association be of the same kind (picture-picture pairs) and same valence  
101 within a given pair, and by using an intentional associative encoding instruction. Our goal was to  
102 elucidate the neural substrates of emotional versus neutral associative memory formation by  
103 focusing on the amygdala, hippocampal and MTL-cortex regions. In relation to previous  
104 neuroimaging studies, several complications in their tasks used to assess emotional association-  
105 memory are addressed with our paradigm. First, emotionally arousing information will inevitably  
106 draw or hold attention. Mixing arousing with non-arousing information in association memory  
107 studies will exaggerate this effect. Bisby et al. (2016) were the only fMRI study using pure  
108 picture pairs. Secondly, a further complication is the combination of different types of  
109 information within an association (e.g., face-occupation pairings in Berkers et al. 2016;  
110 adjective-face pairings in Okada et al., 2011), which alone could have different attentional  
111 demands (see also the relevant source memory studies: Dougal et al., 2007; Kensinger and  
112 Schacter, 2006a) where sources were always neutral and of a different kind than the items).  
113 Finally, the predominant use of incidental encoding instructions cannot address if participants  
114 attended to pair-types in the same or different way. Intentional instructions, explicitly asking  
115 participants to engage in relational encoding, should minimize attentional differences between  
116 pair-types. Although three prior fMRI studies used intentional instructions, two of these (Okada  
117 et al., 2011; Onoda et al., 2009) had a blocked fMRI design disallowing interpretation of

118 resulting brain activity as memory-relevant, and Berkers et al. (2016) asked participants to  
119 simultaneously perform plausibility judgements on each pair. Taken together, we think the  
120 paradigm used here can better assess the involvement in the amygdala and hippocampus in the  
121 impairment of association-memory due to emotion.

122         Based on the extant literature, two alternative neural mechanisms can be hypothesized  
123 that underlie better memory for neutral than emotional pairs. Both hypotheses are based on the  
124 central role of the amygdala in processing emotional arousal and in subsequent modulation of  
125 activity in other brain areas including the medial temporal lobe (MTL) (Sah et al., 2003). Both  
126 hypotheses further implicate the hippocampus and extra-hippocampal MTL-regions, given their  
127 established role in (neutral) associative and item-memory encoding (Diana et al., 2007;  
128 Eichenbaum et al., 2007). According to the first hypothesis, ‘disruption hypothesis’, the  
129 hippocampus remains responsible for association-memory encoding even when dealing with  
130 emotional information. As suggested by several authors, the increase in amygdala activity due to  
131 emotional arousal might lead to a disruption of hippocampus-dependent associative memory  
132 processes, reflected in a decrease in hippocampal activity (Bisby et al., 2016; Murray and  
133 Kensinger, 2014; Okada et al., 2011). This negative effect of amygdala activity on hippocampal-  
134 dependent association-memory formation is also consistent with a dual-representation account:  
135 Better item-memory and worse associative memory for emotional information may be driven by  
136 opposing effects of arousal on amygdala- and hippocampal-dependent memory systems  
137 (Yonelinas and Ritchey, 2015). Opposing effects of emotional arousal on amygdala and  
138 hippocampus, in particular the hypothesized decrease in hippocampal activity, have not yet been  
139 specified (Bisby et al., 2016), although likely indirect (via inhibitory/excitatory connections  
140 between prefrontal cortex and amygdala versus hippocampus, respectively; Tejada and

141 O'Donnell, 2014; Kim et al., 2011; Lee et al., 2012 Moreno et al., 2016). Thus, according to the  
142 disruption-hypothesis, the mechanism underlying the memory disadvantage for negative pairs is  
143 an indirect disruption of hippocampal associative encoding by emotional arousal.

144 Alternatively, the 'bypassing-hypothesis,' is based on the observation that when  
145 associations can be unitized, association-memory can be supported by extra-hippocampal MTL  
146 areas (Haskins et al., 2008; Quamme et al., 2007). Unitization describes the phenomenon that  
147 inter-item associations can be merged under certain conditions to function like *intra*-item  
148 associations or even processed like a single item. Under these circumstances, their encoding  
149 becomes hippocampus-independent and their recognition can be based solely on familiarity (not  
150 episodic recollection; Diana et al., 2008; Ford et al., 2010; Giovanello et al., 2006). Unitization  
151 seems to be a continuous and not an all-or-none process: The degree of unitization depends on  
152 characteristics of the to-be-merged items and the encoding task. For example, it is easier to  
153 unitize the color of a word with the word itself than to unitize two sequentially presented same-  
154 modality items. Similarly, encoding instructions asking for integrative imagery trigger active  
155 unitization attempts more so than non-integrative encoding instructions. Importantly, it has been  
156 shown that two neutral items can be encoded without requiring active unitization attempts or  
157 instruction, for example, if their combination is by itself meaningful or familiar (Ahmad and  
158 Hockley, 2014). Also, if unrelated items belong to the same domain (e.g., face-face pairs)  
159 associative encoding can circumvent hippocampal involvement (Bastin et al., 2010; Mayes et al.,  
160 2007; Mayes et al., 2004; Tibon et al., 2014). Based on this literature, one could hypothesize that  
161 inherently distracting features of emotional items may make them harder to unitize or prevent  
162 extra-hippocampal within-domain associations which then might lead to worse association-  
163 memory (see also: Mather and Sutherland, 2011; Murray and Kensinger, 2013). Accordingly,

164 extra-hippocampal MTL activity may be associated with successful neutral but not with  
165 successful negative pair encoding The bypassing-hypothesis proposes that the mechanism  
166 underlying the memory *advantage* for neutral pairs is additional, extra-hippocampal associative  
167 encoding.

168         Focusing on the amygdala, hippocampus, and extra-hippocampal MTL, different pattern  
169 of results can be predicted according to the two hypotheses. To test the prediction of both  
170 hypotheses, we examined mean activity during emotional and neutral pair encoding irrespective  
171 of subsequent memory as well as subsequent memory effects (SMEs), contrasting brain activity  
172 during encoding of later-remembered (hits) vs. later-forgotten (misses) pairs, separately for  
173 negative and neutral pairs. Both hypotheses converge with respect to predicting a main effect of  
174 emotion in the amygdala: increased amygdala activity during negative than neutral pair  
175 encoding. In addition, both hypotheses also predict a subsequent forgetting effect (greater  
176 activity during subsequently forgotten than remembered pairs) specifically for the negative pairs;  
177 this effect could either be in other parts of the amygdala and/or in stronger coupling between  
178 amygdala activity and other brain regions during subsequently forgotten than remembered  
179 negative pairs. Thus, using psychophysiological interaction analyses, we also tested potential  
180 changes in functional coupling between the amygdala and other brain regions pertaining to  
181 forgetting of negative pairs. The disruption hypothesis would predict then together with higher  
182 amygdala activity decreased mean hippocampal activity levels during negative than neutral pair  
183 encoding. However, this hypothesis would not assume differences in the size of the hippocampal  
184 SMEs: Associative encoding is thought to remain hippocampal-dependent and hippocampal  
185 activity is equally important to subsequent memory-outcome for negative and neutral pairs, just  
186 less likely to occur for the former. Conversely, the bypassing hypothesis assumes given the



187 higher amygdala activity during encoding of negative compared to neutral pairs no difference in  
188 mean-activity levels in the hippocampus. However, because neutral pairs are easier to unitize and  
189 amenable to an alternative, extra-hippocampal strategy, this hypothesis predicts that there should  
190 be additional SMEs in extra-hippocampal MTL, i.e. the MTL cortex, for neutral pairs that are  
191 absent (or weaker) for negative pairs. On an exploratory basis, it might be hypothesized  
192 moreover a decrease in mean MTL-cortex activity as a consequence of emotional arousal during  
193 encoding of negative arousing pairs is observed.

194         Following our behavioural paradigm (Madan et al., 2012), we used intentional  
195 instructions to maximise the potential of association memories to emerge (Hockley and Cristi,  
196 1996). Experiments 1 and 2 confirmed emotional impairment of association-memory alongside  
197 item-memory enhancement (Experiment 2), using a modified procedure of Madan et al. (2012).  
198 As our predictions included different response profiles in putatively adjacent MTL regions—  
199 amygdala, hippocampus, and MTL-cortex—we scanned the MTL using high-resolution fMRI in  
200 Experiment 3. This experiment tests the disruption and bypassing hypotheses with respect to the  
201 predicted roles of the MTL regions during encoding of emotional versus neutral associations.

202

## 203 **2. Materials and Methods**

204 The study was approved by the local ethics committee, Board of Physicians, Hamburg,  
205 Germany. All participants gave written informed consent for this study and received monetary  
206 reimbursement (10 €/h). Figure 1 gives an overview of the common features of all three  
207 experiments.

### 208 *2.1. Experiment 1: Adaptation of Madan et al.'s (2012) procedure for fMRI*

209 Several extensive changes were necessary to adapt the original task (Exp. 1 of Madan et al.,  
210 2012) for fMRI. Briefly, the original procedure was a verbal paired-associates task, presenting  
211 arousing negative and non-arousing neutral words in all possible pairings (pure negative, pure  
212 neutral, and mixed pairs). Participants had been explicitly instructed to learn these as pairs and  
213 were tested with cued-recall after each of 8 sets of 8 pairs. This was followed by a final free-  
214 recall test of all words. Adapting this paradigm for fMRI, we used emotional pictures instead of  
215 words, known to elicit more reliable BOLD responses (Kensinger and Schacter, 2006b).  
216 Furthermore, the two stimuli of a pair were presented simultaneously to avoid problems with  
217 deconvolution of BOLD responses to individual pictures within each pair in the later fMRI task,  
218 and to allow meaningful saccadic eye-tracking recordings. To emulate cued recall but avoid  
219 vocal recordings in the scanner, participants were first asked to covertly recall the associate of  
220 the single probe picture and to make a judgment-of-memory (JoM) with a 2-AFC button-press.  
221 This was followed by 5-alternative-forced-choice (5-AFC) associative recognition.

222

223 **2.1.1. Participants.** A total of 42 healthy male volunteers participated in Experiment 1.

224 Participants were right-handed, had normal or corrected-to-normal vision, and reported no past  
225 or present psychiatric or neurological disorders. Considering the planned fMRI study  
226 (Experiment 3), we selected only males to avoid possible gender-specific lateralization of  
227 amygdala activations in tasks involving emotional materials (e.g., Cahill et al., 2004). Data from  
228 6 participants had to be excluded due to below-chance accuracy in the 5-AFC associative  
229 recognition task. The final group contained 36 participants.

230

231 **2.1.2. Experimental Design.** A total of 320 pictures (160 negative, 160 neutral) were selected  
232 from the International Affective Picture System (Lang et al., 2008) and from the internet. An  
233 independent group of 20 male raters from an unrelated study judged arousal-levels of each  
234 picture on 9-point modified versions of the Self-Assessment-Manikin scales (Bradley and Lang,  
235 1994). With '9' indicating low arousal, pictures preselected as negative (N) were rated higher in  
236 arousal ( $M \pm SD = 5.09 \pm 0.85$ ) than neutral (n) pictures ( $M = 7.70 \pm 0.35$ ;  $t(212) = 35.74$ ,  $p <$   
237  $.001$ ). The experiment was implemented with Presentation (Neurobehavioral Systems Inc.;  
238 Berkeley, CA) software.

239 Experiment 1 comprised three cycles, each with a study phase (Fig. 1A) followed by a  
240 test phase (Fig. 1B). Participants first performed five practice trials, with repeats if needed.  
241 Excluding the practice pictures, a total of 288 pictures (144 negative, 144 neutral) were randomly  
242 selected from the picture pool and presented in three 48-pair cycles.

243

244 Insert Figure 1 here

245

246 In each encoding trial (Fig. 1A), two pictures (450×300 pixels) were shown side-by-side  
247 on a computer screen for 2000 ms (screen resolution 1440×900 pixels), preceded by a fixation  
248 cross for 1000 ms. Pictures were shown simultaneously and pairs included all possible  
249 permutations of negative (N) and neutral (n) pictures on the left side or the right side of a pair  
250 (NN, Nn, nN, nn), as in (Madan et al., 2012), with 12 pairs of each type comprising the 48-pair  
251 cycles. Participants were explicitly asked to study the pairings and informed that their memory  
252 for each pair would be tested later.

253           In the retrieval phase, each pair was tested with a JoM task and a 5-AFC associative  
254 recognition task (see Fig. 1B). One trial in the JoM task lasted 4900 ms, followed by a 100-ms  
255 blank screen and 1000-ms fixation-cross. In the JoM task, pseudorandomized either the left or  
256 right picture of the pair, with no more than two repeats of picture emotion, was presented in the  
257 center of the screen. Participants were prompted by the question: “Recall associate?” and had to  
258 choose a “Yes” or “No” on-screen button with a computer mouse. Participants were asked to be  
259 conservative with their memory judgments and to only endorse a ‘yes’ response if they were sure  
260 they had remembered the previously associated picture of the pair. For the 5-AFC associative  
261 recognition task, the same probe picture was presented in the center of the screen (225 × 150  
262 pixels), surrounded by an array of five pictures (one correct target, four lures) in fixed screen  
263 positions (Fig. 1B). Participants had 3900 ms to choose the target picture from the array with a  
264 computer mouse, followed by a 100-ms blank screen. Lure pictures were always from the just  
265 preceding study phase. The four lures were pseudorandomly selected such that all five  
266 recognition alternatives always had a ratio of 2:3 or 3:2 negative to neutral pictures.

267           An active baseline task was included (Fig. 1C), considering the planned fMRI experiment  
268 (Experiment 3), to prevent high resting state brain activity in regions like the hippocampus and  
269 therefore avoid possible contamination by task-related activity changes in these regions (Stark  
270 and Squire, 2001). Each baseline trial lasted 2000 ms (1900 ms of baseline and 100 ms blank  
271 screen). In each baseline trial, a line drawing of a star was presented in one of five screen  
272 locations (Fig. 1C), analogous to the picture positions in the 5-AFC task (Fig. 1B). Participants  
273 had to select the screen location of the star with the mouse. Two baseline trials were presented  
274 after each study trial in the encoding phase and after each associative recognition trial in the  
275 retrieval phase. In addition to its function as an active baseline task, this procedure also served as

276 a test of the participants' ability to accurately choose between the five screen positions as  
277 required in the 5-AFC task.

278         Prior to each encoding phase and retrieval phase, a pictorial two-back task was used to  
279 clear working memory and to help participants discriminate between different cognitive contexts  
280 (e.g., to separate pictures from the current encoding phase from pictures in earlier encoding  
281 phases; Pastotter et al., 2011). The two-back task consisted of 30 trials and lasted 1 minute. The  
282 task used five line drawings from Rossion and Pourtois (2004), which were presented  
283 sequentially in random order for 1900 ms each, followed by 100 ms of blank screen. Participants  
284 were asked to indicate by button press whether the current drawing was a match or no match to  
285 the drawing shown two trials prior. Figures 1D and 1E give an overview on the timing of events  
286 within the encoding and retrieval phases.

287

288 *2.2. Experiment 2: Concurrent decrease in association-memory and increase in item-memory for*  
289 *negative pictures*

290 In the substantially modified version of the task, Experiment 1 replicated the basic finding of  
291 Madan et al. (2012): an association-memory disadvantage for negative compared to neutral  
292 materials (see Results). Item-memory *enhancement* for emotionally arousing information has  
293 been well-established, including in many fMRI studies (cf. Dolcos et al., 2012). Our previous  
294 study had also identified emotional item-memory enhancement in final free recall (Madan et al.,  
295 2012). The goal of Experiment 2 was to test whether these materials and procedure would also  
296 produce a simultaneous *increase* in a subsequent item-memory test for individual negative  
297 pictures despite a *decrease* in association-memory for negative pairs, similar to our previous  
298 findings (Madan et al., 2012). This required the introduction of an item-memory task in the

299 current design without compromising the intentional associative encoding instruction. The  
300 possibility of applying free recall was complicated by the fact that some of the pictures were not  
301 uniquely describable. Thus, Experiment 2 contained only one study-test block of pictures,  
302 followed by an unannounced 2-alternative-forced-choice (2-AFC) item-recognition memory  
303 task. The 2-AFC task presented a previously encoded picture alongside a new lure picture and  
304 hence did not require associative encoding/retrieval. This design allowed directly contrasting  
305 effects of emotion on association-memory (JoM/5-AFC) with those on item-memory (2-AFC).  
306 Contrary to Experiment 1 which aimed to replicate the findings of Madan et al., (2012), in  
307 Experiment 2 and 3 only pure neutral and negative pairs were employed to gain statistical power  
308 for the comparisons of main theoretical interest. A reduction of conditions was even more  
309 important for the experiments that had fewer possible trials (Experiment 2) or where brain  
310 activity was measured (Experiment 3). Moreover, pure pairs were expected to reduce differential  
311 allocation of attention within a pair.

312

313 **2.2.1. Participants.** A total of 34 healthy male volunteers participated in Experiment 2; six  
314 participants were excluded due to below-chance performance in the item-recognition task,  
315 retaining 28 participants.

316

317 **2.2.2. Experimental Design.** Of the original 320 pictures from the picture pool, 280 (140  
318 negative and 140 neutral) were selected at random for each participant. Of these, 140 (70  
319 negative/70 neutral) were studied during the encoding phase. A higher number of pictures,  
320 compared to encoding blocks in Experiment 1, was necessary to avoid ceiling effects in the 2-  
321 AFC. The remaining 140 pictures were used as lure pictures in the 2-AFC item-memory test.

322 Instead of three encoding-retrieval cycles as in Experiment 1, all 70 pairs were presented in a  
323 single cycle. We presented only pure negative (NN) and pure neutral (nn) pairs in Experiment 2,  
324 with 35 pairs being presented of each type. Asymmetries in recall from mixed pairs in (Madan et  
325 al., 2012) had been attributed to effects of *item*-memory enhancement for negative target words.  
326 Similar asymmetries were detected in Experiment 1 here, using mixed pairs. To reduce the  
327 number of experimental conditions, we presented only pure pairs in Experiment 2. Since only  
328 pure pairs were used, the 5-AFC associative recognition task presented all lures of the same  
329 valence (i.e., the alternatives were five negative pictures or five neutral pictures).

330 The encoding phase, JoM, and 5-AFC associative recognition task were identical to  
331 Experiment 1. Participants were again instructed to intentionally encode the pairs. To probe  
332 item-memory, an unannounced 2-AFC recognition task was included where all items were  
333 tested, preceding the 5-AFC associative-recognition task for all pairs. The 2-AFC task had 140  
334 trials in which a studied, old picture and a non-studied, new lure picture were presented side-by-  
335 side for 2900 ms, followed by a blank screen for 100 ms. The new picture was always of the  
336 same emotional valence as the accompanying old picture. Participants were instructed to select  
337 the studied (old) picture of the two with the computer mouse. The two-back task both preceded  
338 and followed the 2-AFC item-recognition task.

339

### 340 *2.3. Experiment 3: High-resolution fMRI in medial temporal lobe and eye-tracking during study* 341 *of negative and neutral pairs*

342 Experiments 1 and 2 replicated an association-memory reduction for negative information and  
343 simultaneous item-memory enhancement (Madan et al., 2012). Experiment 3 proceeded to test  
344 neural mechanisms underlying both successful and unsuccessful association-memory for

345 negative compared to neutral picture pairs. High-resolution fMRI of the MTL/fusiform regions  
346 was used, concentrating on SMEs, i.e., brain activity during encoding of later successfully  
347 recognized picture pairs (hits) compared to brain activity during encoding of later-forgotten pairs  
348 (misses). In addition, eye-tracking recordings were acquired during encoding to test the potential  
349 link between visual attention patterns and later associative memory success/failure. As  
350 impairment of association-memory for emotional items might be driven by attentional factors,  
351 eye-movements were used as a measure to approximate overt attention.

352

353 **2.3.1. Participants.** A total of 23 healthy right-handed male volunteers participated in  
354 experiment 3. Data from 3 participants were excluded due to below-chance performance in the  
355 associative recognition task, leaving 20 participants.

356

357 **2.3.2. Experimental Design.** A set of 300 pictures was randomly selected from the original 320  
358 pictures for each participant. Similar to Experiment 1, three encoding-retrieval cycles were  
359 carried out. These contained 50 pairs in each cycle (25 of each pair type), with a total of 150  
360 pairs. As in Experiment 2, only pure negative (NN) and pure neutral (nn) pairs were used and all  
361 lure pictures were of the same valence as the target. All other task parameters were identical to  
362 Experiment 1. There was no item-memory task.

363 Eye movements were recorded, using a EyeLink 1000 video-based eye-tracker (SR  
364 Research Ltd.; Mississauga, ON, Canada), at a sampling rate of 1000 Hz and with a spatial  
365 resolution of less than  $0.01^\circ$  and a spatial accuracy of  $0.25^\circ$ - $0.4^\circ$ . An infrared camera located at  
366 the edge of the MRI bed was used to monitor participants' eye movements. Eye-tracking data  
367 were acquired during encoding and retrieval phases, but only encoding data are presented here.



368 Six participants could not be included in the eye-tracking analyses due to issues with the eye-  
369 tracker reliably detecting their pupils during data collection, leaving 14 participants for the eye-  
370 tracking analyses.

371 Pictures were back-projected onto a screen and viewed through a mirror. Instead of a  
372 computer mouse, participants used an MR-compatible joystick (Mag Design and Engineering;  
373 Sunnyvale, CA). MR scanning was conducted during both encoding and retrieval phases, but  
374 only encoding-related brain activity is presented here. To approximate encoding and retrieval  
375 length inside the scanner, the retrieval phase within each cycle was split such that a random set  
376 of 25 pairs out of the 50 pairs from the encoding phase was tested in a first retrieval-phase (12-13  
377 neutral or negative pairs), followed by a second retrieval-phase probing memory for the  
378 remaining 25 pairs. Thus, 9 experimental runs were conducted in total: encoding (50 pairs),  
379 retrieval 1 (25 pairs), retrieval 2 (25 pairs), repeated three times.

380

381 **2.3.3. MRI data acquisition and analysis.** Functional MRI was performed on a 3 T system  
382 (Siemens Trio) with an echo-planar imaging T2\*-sensitive sequence in 36 contiguous axial slices  
383 (1.5-mm isotropic voxels; TR = 2760 ms; TE = 30 ms; flip angle = 80°; field of view = 240×240  
384 mm<sup>2</sup>). The field of view was aligned to the longitudinal axis of the hippocampus and covered the  
385 temporal lobes as well as part of the insular cortex. Figure 3A illustrates the areas covered by the  
386 high-resolution fMRI-sequence. The first five volumes of each functional MR scan were  
387 discarded to allow tissue steady-state magnetization. High-resolution T1-weighted structural MR  
388 image was acquired by using a 3D-MPRAGE sequence (TR = 2300 ms; TE = 2.89 ms; flip angle  
389 = 9°; 1-mm slices; FOV = 256×192; 240 slices).

390 The functional image time-series was slice-time corrected, realigned and corrected for the  
391 interaction of motion and distortion using the unwarp function as implemented in SPM12  
392 (<http://www.fil.ion.ucl.ac.uk/spm>) which corrects the data for movement related signal changes.  
393 Therefore movement regressors were not included in the first level models. Then, the individual  
394 structural T1 image was co-registered to the mean functional image generated during  
395 realignment using an affine rigid-body transformation and the quality of the co-registration was  
396 manually checked for each participant. Co-registered T1 images were segmented using the  
397 ‘Segment’ routine in SPM12. During this step, tissue-class images for gray and white matter  
398 were generated from the structural images and subsequently used with the DARTEL toolbox to  
399 create individual-subject flow fields, which in turn were used for normalization to MNI space.  
400 Functional images were normalized to MNI space using the DARTEL-generated flow fields, re-  
401 sliced with an isotropic voxel size of 1 mm, and smoothed with a Gaussian kernel of 3-mm full-  
402 width at half-maximum (FWHM) .

403 Two sets of analyses were conducted. First, we aimed to identify potential differences in  
404 mean activity, focussing on the hippocampus (disruption hypothesis) and MTL-cortex  
405 (bypassing hypothesis). These analyses included two regressors of interest: neutral and negative  
406 pair encoding. Secondly, we tested four regressors of interest to probe SMEs: activity associated  
407 with neutral hits, neutral misses, negative hits, and negative misses pairs (see also (Caplan and  
408 Madan, 2016)).

409  
410 *2.3.3.1. Mean activity analysis.* In detail, this analysis was aimed at identifying potential  
411 differences in general activity during processing of neutral and negative pairs as suggested by the  
412 disruption hypothesis, i.e., a general decrease in hippocampal activity irrespective of encoding

413 success during processing of negative stimuli (Bisby et al., 2016). First-level models were  
414 constructed for each participant with two regressors modeling the onsets of neutral and negative  
415 pairs using the SPM canonical hemodynamic response function. To derive noise regressors from  
416 voxels unrelated to the experimental paradigm, subject-specific white matter and cerebrospinal  
417 fluid masks were generated based on the segmented T1 images. Principal components explaining  
418 at least 1% of the variance were extracted independently for white matter and cerebrospinal  
419 fluid. These time series were added as nuisance regressors to the first-level models. The  
420 parameter estimates of the two regressors of interest, i.e. activity during processing neutral and  
421 negative pairs, were contrasted at the second level with participant as a random factor to test  
422 whether mean activity in the hippocampus differed in both conditions. Therefore, for each  
423 individual participant the mean activity across all hippocampal voxels in both conditions was  
424 computed. In addition, we also calculated voxel-wise statistics to test whether and where peak-  
425 activity differences were observed within the hippocampal region of interest. Parallel analyses  
426 were conducted focussing on MTL-cortex to probe the bypassing hypothesis. For completeness,  
427 we also report mean activity differences between negative and neutral pair encoding in the other  
428 regions of interests, i.e. the amygdala and fusiform gyrus.

429  
430 *2.3.3.2. Subsequent memory effect (SME) analysis.* Next, we aimed to identify activity  
431 differences during processing of neutral and negative pairs that were related to successful versus  
432 unsuccessful encoding. Thus, another set of first-level models were constructed for each  
433 participant, separating pairs further according to subsequent associative recognition hits versus  
434 misses (an SME based on the 5-AFC task). The subjective recall judgments in the JoM task were  
435 not considered here due to systematic differences between subjective (JoM) and objective (5-

436 AFC) association-memory performance (see Results). The resulting four conditions (negative  
437 associative recognition hits, negative misses, neutral associative recognition hits, neutral misses)  
438 were modeled as separate regressors, again using the canonical hemodynamic response function  
439 as implemented in SPM. The same nuisance regressors as in the first set of first-level models  
440 were included to explain variance related to unspecific noise. In the second-level analyses,  
441 activity related to the pair's emotionality, regardless of later recognition success, was identified  
442 by contrasting negative and neutral pairs (main effect of emotion). Successful association-  
443 memory formation, regardless of the pair's emotionality, was identified by contrasting hits and  
444 misses (main effect of memory; 'subsequent memory effect', SME). The first set of analyses was  
445 agnostic to memory outcome, simply asking whether activity (e.g., in the hippocampus), was  
446 greater or lower during study of NN versus nn pairs. This set of analyses, incorporating memory  
447 outcome, enable us to test whether activity within the regions of interest might relate to memory-  
448 encoding success. One might think that the main effect of emotion in this set of analyses yields  
449 the same information as the mean activity analysis. However, the SME, by its nature, sorts  
450 unequal number of trials into the remembered and forgotten conditions. Because average  
451 accuracy differed between negative and neutral pairs, the main effect of emotion in the SME  
452 analysis is complicated, being a weighted sum of remembered and forgotten trials— where that  
453 weighting differs between conditions. Thus, the main effect of emotion in this set of analyses  
454 should be interpreted with caution; the measure of activity, apart from later memory-outcome,  
455 during study of NN versus nn pairs is directly addressed in the mean activity analysis. To  
456 identify brain regions that separated successful association-memory for negative versus neutral  
457 pairs, we contrasted brain activity associated with the SME in negative versus neutral pairs by

458 applying both interaction contrasts (Emotion×Subsequent Memory Effect: SME negative > SME  
459 neutral; Emotion×Subsequent Memory Effect: SME neutral > SME negative).

460  
461 *2.3.3.3. Psychophysiological interaction (PPI) analysis* . A PPI analysis was conducted, as  
462 implemented in SPM12, to assess task-related differences in functional coupling between brain  
463 regions (Friston et al., 1997). Foreshadowing our results, we tested whether the amygdala  
464 subregion involved in emotional processing (main effect of emotion), was more strongly coupled  
465 during failed encoding of negative pairs with either the hippocampus (disruption hypothesis) or  
466 with extra-hippocampal MTL regions (bypassing hypothesis). Therefore, the seed region was a  
467 left amygdala peak functionally defined at the group-level by contrasting negative vs. neutral  
468 trials of the SME analysis (see Table 2 and Figure 3; main effect of emotion,  $p < .005$ ,  
469 uncorrected, (-19, -7, -15). (Note that the results are consistent when using the amygdala peak  
470 from the main effect analysis (-21 -3 -18), see Results.) The time series, as well as the  
471 interaction of the time series with the psychological factor, hits vs. misses during encoding of  
472 negative pairs, was extracted after adjusting for effects of no interest (including the session  
473 constant and high-pass filter). These two time series were included in the new first-level models  
474 as additional regressors, and the parameter estimates of the interaction regressors were used in a  
475 second-level analysis with participants as a random factor.

476 We also tested whether the differences in functional coupling of the amygdala with the  
477 target region co-varied with performance in the associative recognition task: A stronger negative  
478 influence of the amygdala on encoding-related regions leading to reduced association memory  
479 for negative pairs.

480

481 2.3.3.4. *Regions of interest.* *A priori* regions-of-interest (ROIs) were based on the two hypotheses  
482 of interest. In particular, the amygdalae were selected based on their critical role in processing  
483 emotional arousal and in modulating activity in other brain areas during memory formation  
484 (Dolcos et al., 2012; Murty et al., 2010). The amygdala-MTL network has been described so far  
485 nearly exclusively for emotional item-memory. Nevertheless, these areas were targeted based on  
486 their expected roles in emotional associative memory— although with deviating roles— as  
487 suggested by the few studies on this topic (Bisby et al., 2016; Murray and Kensinger, 2014). In  
488 addition, the hippocampus was chosen based on its well- established role in associative memory  
489 processing (Davachi, 2006; Diana et al., 2007; Eichenbaum et al., 2007) which is proposed to be  
490 disrupted during encoding of emotional pairs according to the disruption hypothesis (Bisby et al.,  
491 2016). The MTL-cortices have been proposed to be involved in memory in a domain-specific  
492 manner, in particular in object memory (perirhinal and lateral entorhinal) versus processing  
493 scenic or spatial context memory (parahippocampal and medial entorhinal) (Eichenbaum et al.,  
494 2012; Schultz et al., 2015; Staresina and Davachi, 2006). The bypassing hypothesis proposes,  
495 based on work on the unitization of associations (Quamme et al., 2007) and on within-domain  
496 associations (Mayes et al., 2007), that neutral pair-associative memory can be formed also in  
497 extra-hippocampal MTL. Unitized pairs of objects or words have been found to be encoded in  
498 the perirhinal cortex (Haskins et al., 2008; Staresina and Davachi, 2010), but the lateral  
499 entorhinal cortex should be also involved (Eichenbaum et al., 2012; Schultz et al., 2015). The  
500 work on within-domain associations suggests that the convergence area of the processing streams  
501 of two items in the MTL should be involved in their associative encoding. For the current scenic  
502 stimulus material, this convergence area would be the parahippocampal and medial entorhinal  
503 cortex. Taken together, based on previous unitization and within-domain association studies, it

504 was not straightforward to predict a priori which one of the extrahippocampal MTL cortical  
505 regions might be most critical for encoding neutral associations here. Therefore, an ROI  
506 comprising all three the MTL-cortices was selected, without further segregation. Finally, two  
507 regions, the insula and the fusiform gyrus, were included as additional ROIs that are not directly  
508 related to the two opposing hypotheses but have been implicated in emotional processing,  
509 respectively encoding. The fusiform gyrus shows not only greater activity during associative  
510 than item encoding in particular for pictures but also reliably shows enhanced activity during  
511 encoding of emotional than neutral information (Kim, 2011; Murty et al., 2010). The part of the  
512 insula included in the scan coverage was selected as an additional ROI because it integrates  
513 emotional and cognitive processes, and is involved in interoceptive awareness of emotions and  
514 bodily states as well as their goal-directed regulation (Chang et al., 2013).

515         ROIs were manually traced on a T1 image, averaged across all participants, after  
516 normalization to MNI space. Ten ROI masks were traced: bilateral amygdala, bilateral  
517 hippocampus, bilateral MTL cortices (perirhinal, entorhinal, parahippocampal), bilateral  
518 fusiform gyrus, bilateral insula cortex (as included in the scanned slices). ROIs were either traced  
519 based on landmarks used in previously published tracing protocols (amygdala, hippocampus,  
520 MTL cortex, fusiform gyrus: Franko et al., 2014; Kim et al., 2000; Pastotter et al., 2011;  
521 Pruessner et al., 2000; Pruessner et al., 2002) using ITK-SNAP v 2.4.0 (Yushkevich et al., 2006)  
522 or published anatomical masks (insula: Deen et al., 2011). Results of all fMRI analyses were  
523 considered significant at  $p < .05$ , family-wise-error (FWE) corrected for multiple comparisons  
524 within the *a priori* anatomical ROIs. For exploratory reasons, we also report clusters present  
525 within the entire scan volume at  $p < .05$ -FWE significance threshold with a minimum cluster  
526 size of 20 mm<sup>3</sup>.

527

528 **3. Results**529 *3.1. Experiment 1: Adaptation of Madan et al.'s (2012) procedure for fMRI*

530 We conducted a  $2 \times 2 \times 2$  repeated-measures ANOVA on the accuracy in the 5-AFC associative  
531 recognition task with within-subjects factors pair-type (pure pairs, mixed pairs), target-type  
532 (negative, neutral), and test direction (forward, backward). Pair-type differentiates whether the  
533 studied pair was a pure pair (nn, NN) or a mixed pair (nN, Nn), target-type differentiates whether  
534 the to-be-recognized target picture was negative or neutral, and test direction differentiates  
535 whether the pair was tested in the forward or the backward direction. For example, encoding a  
536 pair of the type 'nN' shows the neutral picture on the left side on the screen and the negative  
537 picture on the right. Forward testing of such a pair would use the left item, 'n', as the memory  
538 probe picture and asks for recognition of the right item, 'N', as the target picture; backward  
539 testing would show the right 'N' as the probe picture and the left 'n' as the target picture (see  
540 Madan et al., 2010, 2012, and Madan, 2014, for additional details). Test direction was included  
541 to control for potential biases to one side of the screen, such as (right) visual-field preferences for  
542 emotional materials (Natale et al., 1983). Results are shown in Figures 2A and 2B.

543

544 

Insert Figure 2 here

545

546 We observed a significant main effect of pair-type ( $F(1,35) = 6.28, p = .017$ ), as well as  
547 an interaction of pair-type and target-type ( $F(1,35) = 28.55, p < .001$ ). Test direction had no  
548 main effect on associative recognition and was not involved in any interactions (all  $p$ 's  $> .20$ ).  
549 Post-hoc tests on the interaction showed that in pure pairs, negative targets were chosen less



550 accurately than neutral targets ( $t(35) = 4.79, p < .001$ ), extending our previous findings of an  
551 emotional impairment of association-memory with pictures and a forced-choice associative  
552 recognition test, and replicating Bisby et al. (2016). In mixed pairs, negative targets were chosen  
553 more accurately than neutral targets ( $t(35) = 3.07, p < .001$ ). In addition, accuracy was worse for  
554 the pure pairs with a negative target relative to the mixed pairs with a negative target ( $t(35) =$   
555  $2.61, p = .01$ ) and for mixed pairs with a neutral target than for pure pairs with a neutral target  
556 than ( $t(35) = 5.86, p < .001$ ). This pattern of results directly replicates our previous findings:  
557 memory performance was successively worse the more negative items were contained within a  
558 pair, an effect previously linked to associative memory reduction (see Madan et al., 2012).  
559 Furthermore, target retrievability was superior when the target was negative versus neutral,  
560 implying better memory for negative individual pictures, similar to an effect we previously  
561 demonstrated to be caused by negative item-memory advantage.

562         In the JoM task, participants' 'yes' responses, i.e., confidence in their memory, was  
563 analyzed with a simplified repeated-measures ANOVA with trial-type (pure negative, pure  
564 neutral, mixed) as a within-subjects factor. The main effect of trial-type was significant ( $F(2,70)$   
565  $= 14.65, p < .001$ ). Participants were more confident in their memory for pure neutral pairs  
566 ( $M \pm SD = 0.61 \pm 0.20$ ) than pure negative pairs ( $M = 0.50 \pm 0.23$ ), with intermediate memory  
567 confidence in mixed pairs ( $M = 0.55 \pm 0.22$ , Bonferroni-corrected post-hoc  $t$ -tests: all  $p$ 's  $< .05$ ).  
568 5-AFC associative recognition accuracy contingent on JoM response is reported in Table 1. Of  
569 the two measures, 5-AFC associative recognition is a more objective test of memory.  
570 Nonetheless, inclusion of the JoM task makes the retrieval process more similar to cued recall,  
571 and likely makes the task more hippocampal dependent than if the recognition test solely was

572 based on the 5-AFC associative recognition test. Performance in the baseline task was at ceiling  
573 (> 99% correct trials; response time:  $M = 766.69 \pm 133.61$  ms).

574

575 Insert Table 1 here

576

577 The results in the 5-AFC task closely resemble the previous cued recall results (Madan et  
578 al., 2012), namely, a reduction in association-memory for negative pure pairs compared to  
579 neutral pure pairs, with intermediate accuracy for mixed pairs but better performance for  
580 negative targets. Differences in associative memory accuracy (cued recall in Madan et al., 2012)  
581 for different materials can result not just from influences on the association-memory strength, but  
582 from effects on the item-level (see also Madan, 2014; Madan et al., 2010). As outlined in detail  
583 in Madan et al. (2012), our previous computational model formally tested whether association  
584 memory accuracy for negative compared to neutral information was influenced by item-level  
585 parameters ('target retrievability,' 'cue effectiveness') or by the association-memory strength  
586 itself. The results showed that a net-reduction in accuracy for negative pairs was due to an  
587 imbalance of increased item-memory ('target retrievability' model parameter) with a  
588 concomitant, larger, decrease of association-memory strength. Here we nominally replicated our  
589 previous results with the current design. Importantly, the association-memory impairment must  
590 have been large enough to overcome that advantage for negative target-items to produce a net  
591 disadvantage for NN pairs. However, because targets were not explicitly recalled, but rather,  
592 target options were provided to the participant (the 5-AFC procedure), it is possible that these  
593 item-memory effects are not directly related to target-retrievability effects found previously.  
594 Experiment 2 addresses this question directly.

595

596 *3.2. Experiment 2: Concurrent decrease in association-memory and increase in item-memory for*597 *negative pictures*598 In the 2-AFC task, item-recognition accuracy was higher for negative pictures ( $M = 0.92 \pm 0.07$ )599 than neutral pictures ( $M = 0.89 \pm 0.09$ ;  $t(27) = 2.35$ ,  $p = .026$ ; Fig. 2C). As predicted,

600 performance in the 5-AFC task (Fig. 2D) showed the reverse pattern. Since ‘test direction’ had

601 no influence on the results of Experiment 1, we conducted a simplified analysis comparing

602 accuracy between negative and neutral pairs, without test direction. Associative recognition was

603 worse for negative (NN) pairs ( $M = 0.31 \pm 0.22$ ) than neutral (nn) pairs ( $M = 0.38 \pm 0.29$ ;  $t(27) =$ 604  $2.75$ ,  $p = .01$ ) (see Fig. 2B)<sup>1</sup>. In the JoM task, memory confidence for negative and neutral pairs605 was not significantly different ( $t(27) = 1.46$ ,  $p = .16$ ), though confidence for neutral pairs was,606 nominally, slightly higher than for negative pairs (negative:  $M = 0.32 \pm 0.26$ ; neutral:  $M = 0.36 \pm$ 607  $0.27$ ). 5-AFC associative recognition accuracy contingent on JoM response is reported in Table608 1. Performance in the baseline task was at ceiling (> 99% correct trials; response time:  $M =$ 609  $686.98 \pm 125.03$  ms). Thus, Experiment 2 showed that participants were better at item-

610 recognition of negative pictures and thus confirmed positive effect of arousal on the item

611 memory that was suggested by Experiment 1. At the same time participants were worse at

612 associative recognition for negative picture pairs, compared to neutral pictures or neutral pairs,

613 again forming the results of Experiment 1.

614 We next assessed whether these contrasting memory effects were related to each other.

615 Frequencies of individual pictures from each 5-AFC pair that were previously correctly

---

<sup>1</sup> Accuracy was relatively unaffected by only including pairs where both of the items were successfully remembered in the item-memory test: Associative recognition was worse for negative (NN) pairs ( $M = 0.32 \pm 0.23$ ) than neutral (nn) pairs ( $M = 0.39 \pm 0.30$ ;  $t(27) = 3.09$ ,  $p = .005$ ).

616 recognized as items (in the 2-AFC task, i.e.: 0, 1, or 2 pictures) were correlated with later 5-AFC  
617 association-memory success (1) or failure (0), using Yule's  $Q$  as a measure of association, which  
618 is appropriate for dichotomous variables (Warrens, 2008).  $Q$  values range from  $-1$  to  $+1$ , and can  
619 be interpreted much like Pearson correlation. There was no significant relationship between the  
620 two types of memory (negative: 95% CI of Yule's  $Q = (-.32, .22)$ ; neutral:  $Q = (-.12, .31)$ ; CI  
621 was calculated via log-odds transform (Bishop et al., 1975; Hayman and Tulving, 1989). Thus,  
622 better item-memory for negative than neutral pictures was not related to reductions in  
623 association-memory for negative compared to neutral pairs (Fig. 2E), suggesting two different  
624 processes, and replicating the findings of the mathematical model in Madan et al. (2012).

625         In summary, despite substantial changes to the experimental methods from the original  
626 study (Madan et al., 2012), including pictures instead of words, presenting the to-be-associated  
627 stimuli simultaneously, changes to timing, number of pairs in the encoding/retrieval phases, use  
628 of associative recognition instead of cued recall, and the introduction of the JoM task, we were  
629 able to replicate in both experiments the basic finding of interest: Worse associative memory for  
630 negative compared to neutral pairs. In Experiment 2, we further confirmed that this decrease was  
631 accompanied by increased item-memory for negative pictures compared to neutral pictures. The  
632 two effects were not related to each other implying separable influences of emotion on item-  
633 memory and association-memory. Experiment 3 interrogated the roles, during encoding, of  
634 amygdala subregions, hippocampus and other medial-temporal lobe regions in the emotional-  
635 arousal impairment of association-memory.

636

637 *3.3. Experiment 3: High-resolution fMRI in medial temporal lobe and eye-tracking during study*  
638 *of negative and neutral pairs*

639 **3.3.1. Behaviour and eye-tracking.** Mean 5-AFC associative recognition accuracy of the 20  
 640 participants in the fMRI experiment was  $0.55 \pm 0.16$ . Similar to Experiments 1 and 2, associative  
 641 recognition accuracy was lower for negative (NN) pairs ( $M = 0.53 \pm 0.16$ ) than neutral (nn) pairs  
 642 ( $M = 0.59 \pm 0.17$ ;  $t(19) = 3.23$ ,  $p = .004$ ) (Fig. 2F), again reflecting a net impairment of  
 643 association-memory due to emotional arousal. Note that there were similar and sufficient  
 644 numbers of hit and miss trials within each valence, enabling subsequent memory effect analyses  
 645 of the fMRI data. In the JoM task, subjective memory confidence for neutral pairs ( $M = 0.48 \pm$   
 646  $0.16$ ) was not significantly different from confidence for negative pairs ( $M = 0.51 \pm 0.18$ ;  $t(19) =$   
 647  $0.95$ ,  $p = .35$ ). 5-AFC associative recognition accuracy contingent on JoM response is reported  
 648 in Table 1. Performance in the baseline task was at ceiling (98% correct; response time:  $M =$   
 649  $920.58 \pm 129.22$  ms).

650         Although the eye-tracking analyses are underpowered because only 14 participants could  
 651 be analyzed, we included them here to provide additional information about attentional  
 652 differences in processing of neutral and negative pairs. We tested effects of emotion (negative  
 653 pairs, neutral pairs), subsequent memory (hits, misses), and their interaction, on two eye-tracking  
 654 variables: Mean duration of fixations and the number of saccades between the two pictures of a  
 655 pair. We reasoned that increased fixations of a stimulus reflects depth of processing which  
 656 should increase item-memory, whereas increased saccades between pictures may support linking  
 657 them together and increase association-memory. Fixation durations were slightly, although only  
 658 on trend level significance, longer for negative than neutral pairs ( $F(1,13) = 4.10$ ,  $p = .06$ ). There  
 659 was no main effect of memory ( $F(1,13) = 1.55$ ,  $p = .24$ ), nor an interaction between emotion and  
 660 memory ( $F(1,13) = 0.37$ ,  $p = .56$ ) on fixation durations. However, participants made  
 661 substantially fewer saccades between negative pictures of a pair than between neutral pictures

662 ( $F(1,13) = 34.30, p < .001$ ) (Fig. 2G). We also observed more between-picture saccades during  
663 encoding of pairs that were later remembered (i.e., hits vs. misses) — a saccade-based  
664 subsequent memory effect ( $F(1,13) = 5.37, p = .037$ ). The interaction between emotion and  
665 memory on between-picture saccades was not significant ( $F(1,13) = 0.004, p = .95$ ). Thus, the  
666 eye-tracking patterns hinted at deeper processing of negative than neutral images (i.e., longer  
667 fixation duration for negative pictures). Saccadic movements between pictures supported later  
668 association memory: There were more between-picture saccades for subsequently remembered  
669 pairs (hits vs. misses). Importantly there were also fewer between picture saccades for NN than  
670 nn pairs.

671

### 672 **3.3.2. fMRI results.**

673 *3.3.2.1. Mean activity analysis.* The first analysis tested the prediction of the disruption-  
674 hypothesis (Bisby et al., 2016), decrease in hippocampal activity due to emotional arousal.  
675 Because a general rather unspecific decrease in hippocampal activity is proposed by this  
676 hypothesis activity was in a first step averaged across all voxels in the hippocampal ROI. We  
677 observed no evidence for a difference in mean activity in the hippocampal ROIs during  
678 processing negative and neutral pairs, neither in the left nor right hippocampus (left:  $t(19) = 0.00,$   
679  $p = .99$ ; right:  $t(19) = 0.08, p = .94$ ; Fig. 3B). To avoid missing any potential differences in  
680 hippocampal subregions, voxel-wise statistics were computed as well, but these also revealed no  
681 individual voxels with lower activity for the contrast neutral greater than negative in bilateral  
682 hippocampus (all  $ps > .5$ ). Thus, no evidence for the disruption hypothesis was observed. To test  
683 the bypassing-hypothesis, we compared mean activity in the bilateral MTL-cortex ROI which  
684 was lower during negative than neutral pair processing (left:  $t(19) = 6.09, p < .0001$ ; right:  $t(19)$

685 = 3.83,  $p < .005$ ; Fig. 3C) . The voxel-based statistical comparison revealed a significant peak in  
 686 the left MTL cortex (-17 -37 -17),  $Z = 5.44$ ,  $p < .001$ ,  $k_E = 522$ ; and trend in the right MTL  
 687 cortex (15, -36, -12),  $Z = 3.93$ ,  $p = .061$ ,  $k_E = 175$ ). For completeness, we also compared mean  
 688 activity in the fusiform gyrus and amygdala ROIs. In the left fusiform gyrus ROI, mean activity  
 689 was significantly higher during negative than neutral pair encoding ( $t(19) = 2.49$ ,  $p < .05$ )  
 690 whereas the right fusiform showed a trend towards a significant difference ( $t(19) = 1.99$ ,  $p =$   
 691  $.06$ ). Bilaterally, amygdala activity was higher during negative than neutral pair encoding (left:  
 692  $t(19) = 5.59$ ,  $p < .0001$ ; right:  $t(19) = 4.30$ ,  $p < .0001$ ). The voxel-based statistical comparison  
 693 revealed a significant peak in the left (-21 -3 -18),  $Z = 5.79$ ,  $p > 0.001$ ,  $k_E = 552$  and right (24 -1 -  
 694 19),  $Z = 5.90$ ,  $p < 0.001$ ,  $k_E = 451$ ) amygdala. In sum, activity was greater in the amygdala  
 695 during negative compared to neutral pair encoding, equal in the hippocampus, relatively  
 696 decreased in the MTL-cortex and increased in the fusiform gyrus.

697

698 Insert Figure 3 here

699

700 *3.3.2.2. Subsequent memory effect (SME) analysis.* Table 2 summarizes the fMRI findings from  
 701 the analyses that separately modeled effects of both memory and emotion. We observed a main  
 702 effect of memory (SME) in the left fusiform cortex and the right amygdala, showing greater  
 703 activity during successful association-memory encoding than during unsuccessful encoding.  
 704 Additional trends for a SME main effect within the ROIs included activations in the left  
 705 amygdala, left hippocampus, and right fusiform cortex.

706

707

Insert Table 2 here

708

709 We further observed a pronounced main effect of emotion. Regardless of later association-  
710 memory success, increased activity was observed during encoding of negative pairs than neutral  
711 pairs in large clusters of the bilateral insula (left insula: Fig. 4A) and bilateral amygdala (left  
712 amygdala: Fig. 4D). Note that the latter contained the smaller amygdala regions associated with  
713 the memory main effect (SME; see Table 2), confirmed by two conjunction analyses (right  
714 amygdala: (22, -2, 21);  $Z = 3.98$ ,  $p = .03$ ,  $k_E = 30$ ; left amygdala: (-17, -8, -14);  $Z = 3.72$ ,  $p =$   
715  $.065$ ,  $k_E = 23$ ). Insula activity was localized more specifically to the dorsal and ventral anterior  
716 insula according to the connectivity-based atlas by (Deen et al., 2011). The reverse main effects  
717 (memory (misses > hits); emotion (neutral > negative)), did not reveal activations within the  
718 ROIs, but additional whole-brain results are listed in Table 2.

719 Participants with a stronger amygdala main effect to negative pairs also tended to visually  
720 fixate on individual negative pictures longer than neutral pictures ( $r = .51$ ,  $p = .063$ ) and to make  
721 fewer saccades between them ( $r = -.47$ ,  $p = .09$ ), although these correlations reached only trend-  
722 level significance due to reduced statistical power.

723

724

Insert Figure 4 here

725

726 Critically, we observed an emotion by memory interaction in various ROIs (see Table 2).  
727 Inspecting the interaction, successful encoding of negative pairs versus neutral pairs was  
728 associated with increased activity in two left hippocampal areas, one anterior and one posterior  
729 (Poppenk et al., 2013), and in bilateral insula. The insula peaks were located in its posterior part  
730 according to (Deen et al., 2011). Activity in the left insula and in the anterior left hippocampal



731 cluster are shown in Figures 5B and 5C, respectively. These effects were driven by an SME for  
732 negative rather than a subsequent forgetting effect (SFE) for neutral pairs as the bar plots show.

733

734 Insert Figure 5 here

735

736 Formal follow-up of these interactions showed that there was significantly more activity  
737 for remembered than forgotten negative pairs in the hippocampus (anterior  $Z = 4.62$ ,  $p = .005$ ;  
738 posterior  $Z = 4.43$ ,  $p = 0.12$ ) and a trend in the insula ( $Z = 3.66$ ,  $p = .087$ ), but no such  
739 differences for neutral pairs (insula:  $Z = 2.45$ ,  $p = .84$ ; anterior hippocampus:  $Z = 1.30$ ,  $p = .99$ ;  
740 posterior hippocampus:  $Z = 0.77$ ,  $p = .99$ ;  $p$ -values FWE-corrected for multiple comparisons).

741 In contrast, unsuccessful encoding of negative pairs versus neutral pairs was associated  
742 with decreased activity in a ventral region of the left amygdala (see Fig. 4C,E), distinguishable  
743 from the more central/dorsal amygdala region observed in the main effect of emotion (Fig. 4D),  
744 as well as in left MTL-cortex (Table 2). We then formally tested whether the interaction effect  
745 in the ventral amygdala more likely represented an SFE to negative pairs or an SME to neutral  
746 pairs. That is, we contrasted activity in the two amygdala localizations that showed the  
747 interaction effect  $(-27, -6, -28)$  and  $(-22, -6, -27)$  (Table 2). These rendered some evidence for  
748 significant activation differences between remembered and forgotten negative pairs, but no such  
749 differences for neutral pairs (negative:  $Z = 3.83$ ,  $p = .046$ ;  $Z = 3.04$ ,  $p = .39$ ; neutral:  $Z = 1.76$ ,  $p$   
750  $= .99$ ;  $Z = 2.71$ ;  $p = .63$ ;  $p$ -values FWE-corrected for multiple comparisons). Thus, ventral  
751 amygdala activity, at least in one of the two identified regions  $(-27, -6, -28)$ , more likely  
752 represents an SFE for negative pairs than an SME for neutral pairs (Fig. 4E).

753           The same logic applied to the interaction effect in the MTL cortex (Fig. 5E). Probing  
 754 whether this interaction was driven rather by an SME for neutral or by an SFE for negative pairs  
 755 revealed no significant effects in either of the pair types. Nevertheless, nominally, the pattern of  
 756 differences implied more of a neutral SME ( $Z = 3.71, p = .11$ ;  $p$ -values FWE-corrected for  
 757 multiple comparisons), whereas the negative SFE was not significant ( $Z = 2.06, p = .9$ ). Thus,  
 758 the significant interaction was more likely driven by an SME for neutral than by an SFE for  
 759 negative pairs. Interestingly, the MTL-cortex interaction peak (-17, -31, -17) was localized very  
 760 close to the MTL-cortex peak that showed decreased activity due to negative emotion in the first  
 761 set of fMRI analyses (-17, -37, -17) (compare Fig. 3C and Fig. 5E).

762           Thus, we observed two spatially separable left amygdala activation foci: (a) a more  
 763 central location associated with negative picture processing irrespective of later memory, and (b)  
 764 a more ventral location associated with unsuccessful encoding of negative pairs. In addition, we  
 765 observed an area in the left MTL-cortex where activity correlated more with successful encoding  
 766 of neutral than of negative pairs.

767

768 *3.3.2.3. Psychophysiological interaction (PPI) analysis.* To test whether there were differences  
 769 in functional coupling during the processing of negative pairs related to differences in  
 770 subsequent memory success, a PPI analysis was conducted using the functionally defined left  
 771 central/dorsal<sup>2</sup> amygdala peak (-19, -7, -15) (Table 2) as a seed region. The PPI identified an area  
 772 in ventral amygdala (-28, -5, -29) ( $Z = 3.40, p = .046$ , small-volume-corrected (SVC) based on a  
 773 sphere with 5-mm radius around the peak activation of the interaction analyses reported above)

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<sup>2</sup> ‘Central’ and ‘ventral’ amygdala here refer to peak locations within the amygdala ROI. These terms are not meant to imply we measured activity in the central and ventro-lateral nuclei of the amygdala, which cannot be reliably distinguished with the current MRI parameters.

774 that exhibited stronger functional coupling with the left central/dorsal amygdala seed during  
775 encoding of later-forgotten negative pairs than later-remembered negative pairs (i.e., misses >  
776 hits). As can be seen in Figure 4, the identified PPI interaction effect spatially overlapped the left  
777 ventral amygdala (-27, -6, -28) peak that had shown significant activation differences between  
778 remembered and forgotten negative pairs. (We additionally conducted a parallel PPI analysis  
779 using the central/dorsal amygdala peak from the mean activity analysis (two-regressor model) (-  
780 21, -3, -18) and similarly found a ventral amygdala cluster (-27, -3, -30) ( $Z = 3.24, p = .048$ .)  
781 Central/dorsal amygdala activity (negative picture processing) and ventral amygdala activity  
782 (unsuccessful encoding of negative pairs) were further positively correlated ( $r = .47, p = .036$ )  
783 across subjects. The functional coupling between central/dorsal and ventral amygdala during  
784 unsuccessful negative pair encoding was indeed also stronger in people with larger reductions in  
785 association memory for negative compared to neutral pairs, although the correlation was only a  
786 trend ( $r = .41, p = .069$ ).

787

#### 788 **4. Discussion**

789 In three experiments, we observed consistently lower association-memory for negative compared  
790 to neutral pictures in paired-associate tasks. The magnitude of this reduction was comparable  
791 across the current experiments (Experiments 1–3: 8.56%, 6.84%, 6.21%, respectively) and the  
792 original verbal design (Madan et al., 2012: 7.73%). In addition, we also observed the well-  
793 established emotional item-memory enhancement (Experiments 1 and 2). The disruption-  
794 hypothesis, that arousal-induced amygdala activity results in decreased hippocampal activity,  
795 presumably via the PFC, was not supported. Results were instead consistent with the bypassing-  
796 hypothesis: We observed substantially decreased MTL-cortex activity during processing of

797 negative pairs and a stronger SME for neutral pairs in an adjacent area of left MTL-cortex (Fig.  
798 5E). Left hippocampal activity (Fig. 5C) was *increased* during encoding of later successfully  
799 remembered negative pairs, a finding that was not predicted by either of the two hypotheses.  
800 This finding is compatible only with the bypassing-hypothesis, because the disruption-hypothesis  
801 explicitly assumes a decrease of hippocampal activity during emotional association-memory  
802 encoding (irrespective of encoding success). Moreover, we were able to dissociate two amygdala  
803 clusters with distinct response profiles, one in the central/dorsal amygdala linked to negative  
804 picture processing irrespective of associative memory encoding success (Fig. 4D) and the other  
805 in the lateral/ventral amygdala showing an SFE for negative pairs (Fig. 4C and 4E). The current  
806 results suggest that two parallel mechanisms produce the associative memory advantage for  
807 neutral over negative pairs: One in the MTL-cortex that exclusively supports successful encoding  
808 of neutral pairs, and one in the hippocampus that exclusively supports encoding of negative  
809 pairs. This could imply that during negative pair encoding, association-memory supporting  
810 hippocampal contributions can only partly compensate for the absence of MTL-cortical  
811 contributions, resulting in a net-decrease in association memory for negative pairs.

812

#### 813 **4.1. Neural substrates of emotional associative memory**

814 There is a relatively sparse and methodologically heterogeneous previous fMRI literature  
815 on inter-item emotional associative memory (Bisby et al., 2016; Curcic-Blake et al., 2012;  
816 Murray and Kensinger, 2014; Okada et al., 2011). The main advance of the current study is the  
817 use of a robust and behaviorally grounded paradigm, with multiple replication across  
818 experiments. Asking participants directly to encode the associations was rarely done in this field  
819 (Berkers et al., 2016; Okada et al., 2011; Onoda et al., 2009), with none of these studies

820 investigating subsequent memory effects. The only other study using negative picture-picture  
821 pairs (Bisby et al., 2016) aimed to test and found support for the disruption hypothesis, implying  
822 that increased amygdala activity may disrupt hippocampal activity during negative association  
823 memory formation. However, we observed *more* rather than less hippocampal engagement  
824 during successful formation of emotional associative memories, which suggests continued and  
825 additional engagement of the hippocampus in this difficult task. Identifying subregions within  
826 the amygdala that participated in emotional processes versus those involved in forgetting effects  
827 further offers novel evidence for neural substrates underlying inferior emotional association  
828 memory.

829       Bisby et al. (2016) interpreted their results as support for the disruption-hypothesis.  
830 Briefly, they reported emotional association memory reductions accompanied by reduced  
831 anterior hippocampal activity during encoding of negative pairs. Ventral-lateral left amygdala  
832 activity promoted subsequent *item*-memory for negative pictures. Together, these results were  
833 suggestive of an amygdala-based disruption to hippocampal associative encoding, concurrent  
834 with increases to emotional item memory. Methodological differences between Bisby et al. and  
835 our study (Exp. 3) may have driven the differences in findings. Notably, Bisby et al. (2016)  
836 reported no amygdala main effect to negative pairs, unlike the robust dorsal/central amygdala  
837 main effect here. This could point to differences in the scanning resolution and statistical power  
838 between studies, the emotional nature of the materials, and/or the emotional involvement of  
839 participants (who encoded pairs incidentally in Bisby et al., 2016). Further, the item-memory  
840 effect (showing the amygdala-related SME in Bisby et al., 2016) appears to have been based on  
841 successful item-memory, but may have included failed association memory responses. As we  
842 further did not test item-memory in Experiment 3, these factors taken together make a direct

843 comparison with the current results difficult. Despite these differences, our results cannot  
844 support the conclusion that amygdala activity disrupted hippocampal associative memory  
845 functions.

846

## 847 **4.2. Amygdala**

848 The amygdala played a major role in our findings, pointing to differentiable within-  
849 amygdala localizations. Negative pictures were linked to stronger central/dorsal activity  
850 irrespective of memory. Failed encoding of negative pairs was related to left ventral amygdala  
851 activity. Critically, these two effects were functionally coupled, with stronger coupling during  
852 encoding of subsequently forgotten than remembered negative pairs as revealed by the PPI  
853 where the strength of this coupling marginally correlated with lower negative association-  
854 memory performance. Moreover, across participants, those with a larger ventral amygdala SFE  
855 also showed more central/dorsal amygdala activity to negative pairs.

856 According to a recent high-resolution fMRI study that aimed to dissociate amygdala  
857 subregions, the central/dorsal amygdala cluster identified in our study maps on the basal and  
858 centromedial groups, whereas the ventral cluster in our study maps on the lateral nucleus  
859 (Hrybouski et al., 2016). Only the centromedial, and to a lesser extent, the basal groups, but not  
860 the lateral nucleus, showed enhanced activity in response to negative pictures in Hrybouski et al.  
861 (2016), mirroring the response profiles in our study. Based on this combined anatomical and  
862 functional consistency, the central/dorsal cluster in our study might reflect activity of the  
863 centromedial group and the ventral cluster maps onto the lateral nucleus. The centromedial group  
864 receives direct and indirect (via the lateral and basal amygdala) projections from nearly all brain  
865 region, in particular from the sensory and prefrontal/orbitofrontal cortex regions and is the main

866 output region of the amygdala, in particular it also modulates the lateral amygdala (Sah et al.,  
867 2003). The lateral amygdala in turn shows - similar to the basal part - strong bidirectional  
868 connectivity with the hippocampus and other MTL regions and modulates prefrontal cortex  
869 (PFC) (Sah et al., 2003). Acknowledging that even the current high resolution fMRI sequence  
870 cannot reliably distinguish sub-amygdalar nuclei, our findings imply that stronger centromedial  
871 amygdala responses to negative pairs triggered lateral amygdala activation which then disturbed  
872 association-memory formation (via its known projections to the PFC, modulating MTL activity).  
873 Future studies including PFC regions should test these suggestions more directly.

874         The eye-tracking results complement our interpretations of the activity patterns in the  
875 amygdala. Longer fixation durations for negative pictures were trend-correlated with  
876 central/dorsal amygdala activity. This might reflect an attentional bias towards individual  
877 negative pictures, leading to an emotional item-memory advantage (see Experiment 2; Markovic  
878 et al., 2014; Pourtois et al., 2013). In contrast, inter-item saccades— a proxy for the distribution  
879 of attention between both pictures— supported associative memory. Fewer such saccades were  
880 made during negative- than neutral-pair encoding (Fig. 2G) and participants with more  
881 central/dorsal amygdala activity to negative pictures also tended to make fewer saccades between  
882 them. Thus, emotional arousal might elicit bottom-up attentional processes (longer fixation  
883 duration) interfering with attentional processes (fewer saccades) that serve associative encoding,  
884 for example, incidental unitization. However, overt attentional processes engaged in *attempts* to  
885 encode a pair appear similar regardless of pair-valence, since we did not observe an interaction  
886 between emotion and memory in the eye-tracking results. Although these attentional  
887 interpretations appear plausible, the eye-tracking results and trends are limited due to low power.  
888

### 889 **4.3. MTL cortex and hippocampus**

890 MTL-cortex activity at the border between entorhinal and parahippocampal cortex was  
891 decreased during negative pair encoding (Fig. 3C) and an area in close proximity was related to  
892 successful encoding of neutral, but not negative pairs (Fig. 5E). These results are predicted by  
893 the bypassing hypothesis and consistent with findings of non-hippocampal MTL contributions to  
894 formation of neutral association memory. Previous studies have suggested better memory for  
895 unitized associations in extra-hippocampal MTL cortex, in particular perirhinal cortex. Using  
896 verbal materials (Ford et al., 2010; Giovanello et al., 2006; Haskins et al., 2008; Quamme et al.,  
897 2007; Staresina and Davachi, 2010) these studies have also shown that unitization can be  
898 triggered by as little as forming a combined sentence or artificial compound word. However,  
899 irrespective of unitization instructions, Mayes et al. (2004; 2007) suggested that certain types of  
900 associations, namely within-domain associations, can be formed by extra-hippocampal MTL  
901 regions. According to this work, items can be associated as soon as their processing streams  
902 converge in the MTL. For *between*-domain associations, this can only be accomplished by the  
903 hippocampus. For within-domain associations, extra-hippocampal regions would be sufficient.  
904 The target regions of convergence here, processing two pictures with scenic content, would be  
905 the parahippocampal and entorhinal cortices (Eichenbaum et al., 2012; Schultz et al., 2015).  
906 Based on these literatures we suggest that the association-memory advantage for neutral pairs  
907 could have been driven by better incidental unitization of neutral than negative scenes or more  
908 efficient within-domain associative processes, subserved by parahippocampal/entorhinal cortex  
909 regions.

910 In addition to evidence in support of the bypassing-hypothesis, we observed hippocampal  
911 activity supporting associative encoding of negative pairs. We propose that when sufficiently



912 arousing information precludes unitization-based or within-domain associative encoding  
913 supported by MTL-cortex regions, an alternative, relational hippocampus-dependent encoding  
914 strategy may be engaged. Findings outside the emotional memory literature suggest increased  
915 hippocampal involvement during encoding with higher memory demands during retrieval (i.e.,  
916 recollection vs. familiarity, recall vs. recognition, source memory, memory for contextual details,  
917 etc.; Beylin et al., 2001; Eichenbaum et al., 2012; Rugg et al., 2012; Smith et al., 2011). Thus,  
918 despite the detrimental influence of emotional arousal on associative encoding, negative (but not  
919 neutral) pairs accompanied by additional hippocampal activity during encoding were more likely  
920 remembered, suggesting that hippocampal activity is partly compensatory.

921

#### 922 **4.4. Insula**

923 In addition to the MTL regions we focussed on, memory-relevant activations included  
924 those in bilateral insula during negative-pair encoding, and in particular, posterior insula during  
925 *successful* encoding of negative pairs. Posterior insula, functionally connected with primary and  
926 secondary somatomotor cortices is typically related to physical sensations (e.g., pain; Chang et  
927 al., 2013). An fMRI meta-analysis by Uddin et al. (2014) illustrated in addition, that apart from  
928 substantial co-activation of insular divisions across many tasks and studies, unique activation of  
929 the posterior (but not anterior) insula showed a particular involvement in interoceptive awareness  
930 (see Uddin et al., 2014). In the current study, posterior insula activity during successful negative-  
931 pair encoding could reflect awareness of one's own emotional response to the negative pictures  
932 or regulation thereof (Lane et al., 1997; Pollatos et al., 2007; Tsuchiya and Adolphs, 2007; Zaki  
933 et al., 2012). Thus, in the current study, successfully forming association memories between two

934 negative pictures could have required down-regulation of internal emotional states evoked by the  
935 individual pictures.

936

#### 937 **4.5. Conclusions**

938 Association memory for negative information was consistently impaired. Negative information  
939 triggered higher central amygdala activity, which modulated ventral-lateral amygdala regions  
940 directly linked to failed negative-pair encoding. Only neutral pair encoding benefited from extra-  
941 hippocampal contribution, possibly due to easier unitization of neutral than negative information.  
942 Counter to previous suggestions, hippocampal activity was not disrupted during negative-pair  
943 learning. Instead (left) hippocampus may provide a compensatory role if extra-hippocampal  
944 association memory support is not available, supporting association-memory for negative pairs.  
945 This increased hippocampal engagement during negative pair learning may partly offset  
946 detrimental association memory influences of the amygdala.

947

948

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- 1152

1153 **Table 1: 5-AFC associative recognition accuracy ( $M \pm SD$ ) contingent on judgement-of-**  
 1154 **memory (JoM) response, for all experiments.**

<b>Pair Type</b>	<b>JoM=Yes</b>	<b>JoM=No</b>	<b><i>t</i></b>	<b><i>p</i></b>
<i>Experiment 1</i>				
Pure Negative (NN)	0.83 ± 0.19	0.47 ± 0.22	7.33	< .001
Pure Neutral (nn)	0.87 ± 0.13	0.44 ± 0.19	10.17	< .001
Mixed	0.80 ± 0.17	0.43 ± 0.18	10.53	< .001
<i>Experiment 2</i>				
Pure Negative (NN)	0.47 ± 0.35	0.24 ± 0.16	3.49	< .01
Pure Neutral (nn)	0.47 ± 0.38	0.29 ± 0.20	3.56	< .01
<i>Experiment 3 (fMRI)</i>				
Pure Negative (NN)	0.72 ± 0.18	0.35 ± 0.16	11.66	< .001
Pure Neutral (nn)	0.83 ± 0.10	0.36 ± 0.16	14.06	< .001

1157  
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1159 **Table 2:** Regions of interest and whole-brain ANOVA results for the effects of emotion and  
 1160 memory  
 1161

Region	Peak coordinates (x, y, z)	Z-statistic	Significa nce	Voxel extent (at $p$ = .005)
<b>ROI, small-volume corrected (<math>p &lt; .05</math>)</b>				
<i>Subsequent Memory Effect (SME: Hits &gt; Misses)</i>				
right amygdala	22, -2, -21	3.86	$p = .047$	23
left fusiform	-39, -18, -28	4.13	$p = .023$	47
left amygdala	-17 -9 -13	3.80	$p = .054$	21
left hippocampus	-18 -18 -18	3.90	$p = .088$	32
right fusiform	24 -47 -20	3.91	$p = .073$	28
<i>Emotion (Negative &gt; Neutral)</i>				
left amygdala	-19, -7, -15	5.41	$p < .001$	489
right amygdala	23, -2, -20	5.52	$p < .001$	362
left insula	-42, -4, -1	5.35	$p < .001$	643
right insula	40, 0, -4	5.27	$p < .001$	246
right insula	39, -13, 6	4.08	$p = .024$	31
right insula	38, 8, -10	3.95	$p = .037$	121
<i>Emotion x Subsequent Memory Effect</i> (negative: hits > misses) > (neutral: hits > misses)				
left hippocampus	-24, -16, -15	4.63	$p = .006$	39
left hippocampus	-27, -36, -7	4.47	$p = .011$	45
left insula	-45, -11, -1	4.08	$p = .021$	129
right insula	38, -7, -4	4.06	$p = .025$	22
<i>Emotion x Subsequent Forgetting Effect</i> (negative: hits > misses) < (neutral: hits > misses)				
left amygdala	-27, -6, -28	3.95	$p = .033$	20
left amygdala	-22, -6, -27	3.88	$p = .045$	30
left MTL cortex	-17, -31, -17	4.03	$p = .040$	17

Region	Peak coordinates (x, y, z)	Z-statistic	Significance	Voxel extent (at $p = .005$ )
<b>Whole-brain (FWE, <math>p &lt; .05</math>)</b>				
<i>Subsequent Forgetting Effect (Misses &gt; Hits)</i>				
right temporo-parietal junction	50, -51, 31	4.33	$p = .004$	203
left precuneus	8, -73, 35	5.82	$p < .001$	5465
<i>Emotion (Negative &gt; Neutral)</i>				
left inferior temporal gyrus	-45, -49, -15	inf (t = 10.53)	$p < .001$	439
right inferior temporal gyrus	44, -60, -9	inf (t = 10.2)	$p < .001$	1882
right middle occipital	27, -73, 35	5.76	$p = .002$	2349
right thalamus	45, -17, -1	5.31	$p = .024$	637
right hippocampus	23, -41, -2	5.26	$p = .031$	123
<i>Emotion (Neutral &gt; Negative)</i>				
left precuneus	-16, -61, 19	7.07	$p < .001$	12834
right angular gyrus	41, -66, 42	5.97	$p = .001$	3785
left fusiform	-24, -46, -9	5.91	$p = .001$	1762
left middle occipital gyrus	-33, -84, 36	5.50	$p = .010$	2335
right precuneus	2, -64, 44	5.20	$p = .040$	1302

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1164 **Figure Captions**

1165

1166 **Figure 1:** Experimental procedure of the encoding tasks and associative recognition tasks used  
 1167 in all three experiments. (A) Encoding task with an example trial of a neutral-neutral (nn) pair.  
 1168 B) Recognition task. (C) Baseline task. (D) Timing of the encoding task. (E) Timing of the  
 1169 recognition task. 5-AFC: Five Alternative-Force-Choice associative recognition task; JOM:  
 1170 Judgement of Memory task. In Experiment 2, a 2-AFC item-recognition task for all items  
 1171 occurred between encoding and the 5-AFC associative recognition task for all pairs.

1172

1173 **Figure 2:** Behavioral results from Experiments 1–3. (A) Accuracy in the associative recognition  
 1174 task (5-AFC) for all negative (NN) and neutral (nn) pairs in Experiment 1. (B) Associative  
 1175 recognition accuracy from all four conditions in Experiment 1: pure negative (NN), pure neutral  
 1176 (nn), and mixed pairs (nN, Nn). For each pair of bars, the left-hand bar plots the forward probe  
 1177 and the right-hand bar plots the backward probe. Gray bars indicate neutral target pictures, red  
 1178 bars indicate negative target pictures. Observe that accuracy for Nn backward is nearly  
 1179 equivalent to nN forward (these tests both have a neutral probe item and a negative target item).  
 1180 Likewise, accuracy is nearly equivalent for Nn forward and nN backward (these tests both have a  
 1181 negative probe and a neutral target) - in turn, lower than Nn-backward and nN-forward. This is  
 1182 what one expects if there is an emotional enhancement of item-memory dependent on the  
 1183 characteristic of the target. That is, both nN and Nn pairs have the same pair composition: one  
 1184 Negative and one Neutral item; thus, within these pairs, there is evidently an effect of item-  
 1185 memory. If we assume that this emotional enhancement of target-item memory is present as well  
 1186 for pure pairs, then the fact that accuracy for nn > accuracy for NN (regardless of probe  
 1187 direction) suggests that there is an emotional impairment of memory for the association that not  
 1188 only cancels out, but surpasses, in magnitude, the emotional enhancement of item-memory. See  
 1189 Madan et al. (2010, 2012) for more discussion of how to interpret such data plots, as well as  
 1190 examples of mathematical model-fits that support these interpretations. (C) Item recognition  
 1191 accuracy in Experiment 2. (D) Associative recognition accuracy in Experiment 2. (E) Proportion



1192 of pairs from Experiment 2 in which two, one, or none of the individual pictures were recognized  
 1193 in the item recognition task, split by associative recognition hits vs. misses. The lack of  
 1194 difference between association-correct and association-incorrect shows that there was no  
 1195 relationship between item- and association-memory. This argues against the possibility that a  
 1196 strong emotional item is the cause of the disruption of association-memory. (F) Associative  
 1197 recognition accuracy in Experiment 3 (fMRI). (G) Mean number of saccades between the two  
 1198 pictures of a pair in Experiment 3 for remembered (Hit) and forgotten (Miss) negative (NN) and  
 1199 neutral (nn) pairs. Chance level in the 5-AFC associative recognition task was  $1/5 = 0.20$  (panels  
 1200 A, B, D, F). Chance level in the 2-AFC forced choice item-recognition task was  $1/2 = 0.50$   
 1201 (panel C). Error bars are 95% confidence intervals around the mean, corrected for inter-  
 1202 individual differences (Loftus and Masson, 1994).

1203

1204 **Figure 3:** MRI acquisition and region-of-interest (ROI) results from Experiment 3. (A) Sagittal  
 1205 and coronal sections from the MPRAGE anatomical volume ( $1 \text{ mm}^3$ ) illustrating the functional  
 1206 scan coverage in the fMRI study. Mean encoding activity for (B) hippocampal and (C) MTL  
 1207 cortex ROIs, regardless of memory outcome.

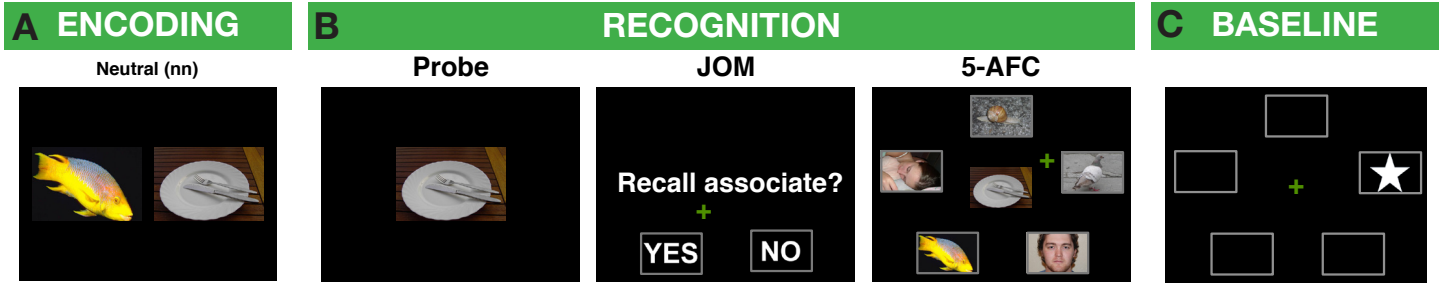
1208

1209 **Figure 4:** Activations and beta estimates from Experiment 3. (B) Coronal slice showing  
 1210 activation clusters. (A) Main effect of emotion in the left insula and (D) left central amygdala.  
 1211 (C,E) Emotion x SME interaction in the left ventral amygdala. Conditions are denoted as  
 1212 negative-negative (NN) or neutral-neutral (nn) pairs that were either hits or misses in the  
 1213 associative recognition task. PPI = psychophysiological interaction analysis with left  
 1214 central/dorsal amygdala seed. Blue region indicates a ventral amygdala region showing  
 1215 significant functional coupling to the seed region,  $p = .04$ , small-volume-corrected.

1216

1217 **Figure 5:** Subsequent memory effects (SME) interaction results from Experiment 3. (A) Coronal  
1218 slice showing the SME clusters specific to negative pairs. Beta estimates are shown for clusters  
1219 in the (B) left posterior insula and (C) left hippocampus. (D) Coronal slice showing SME clusters  
1220 specific to neutral pairs. (E) Beta estimates for cluster in the left MTL cortex.  
1221  
1222

Figure 1



**PROCEDURE**

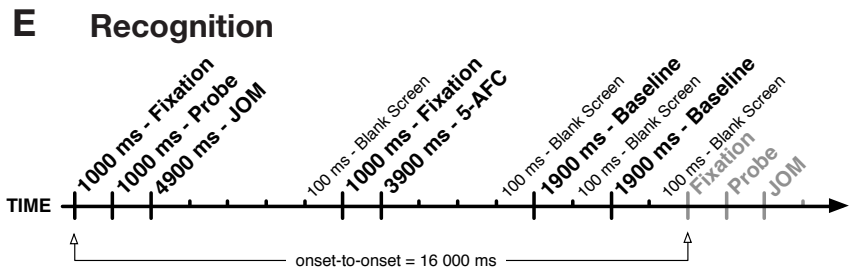
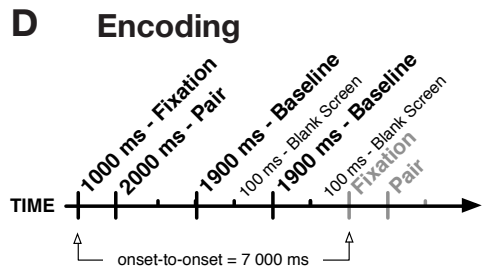
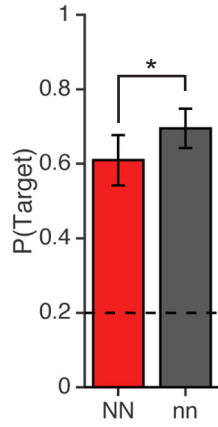


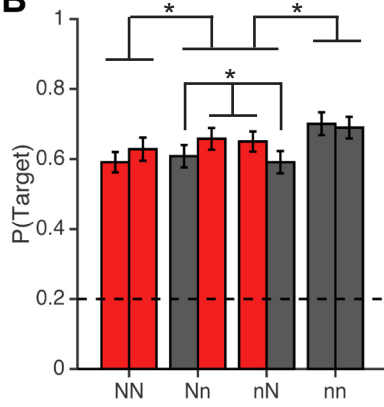
Figure 2

### EXP 1

**A**

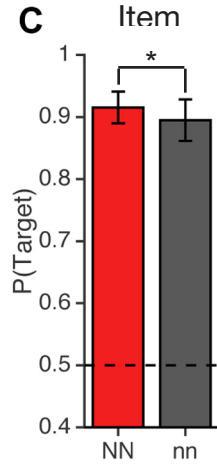


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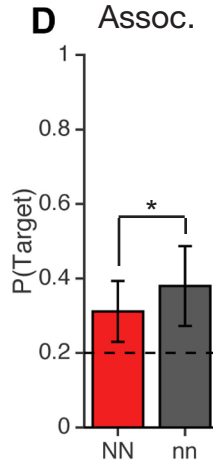


### EXP 2

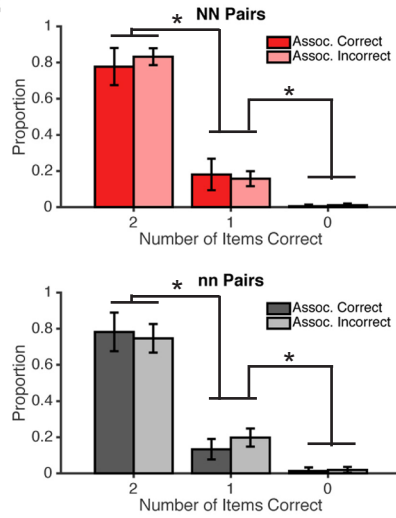
**C**



**D**

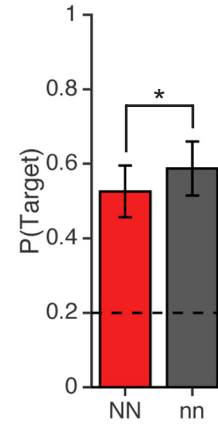


**E**



### EXP 3 (fMRI)

**F**



**G**

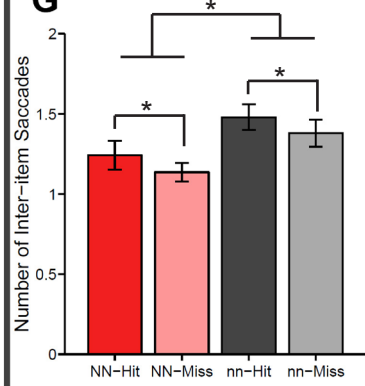


Figure 3

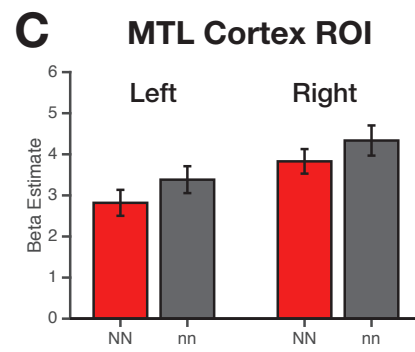
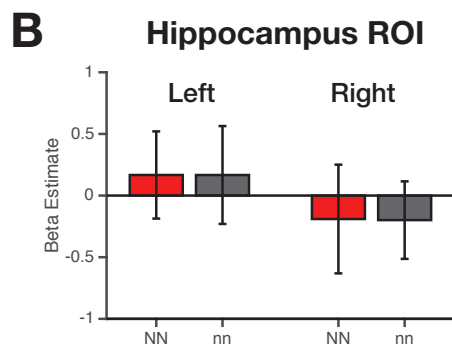
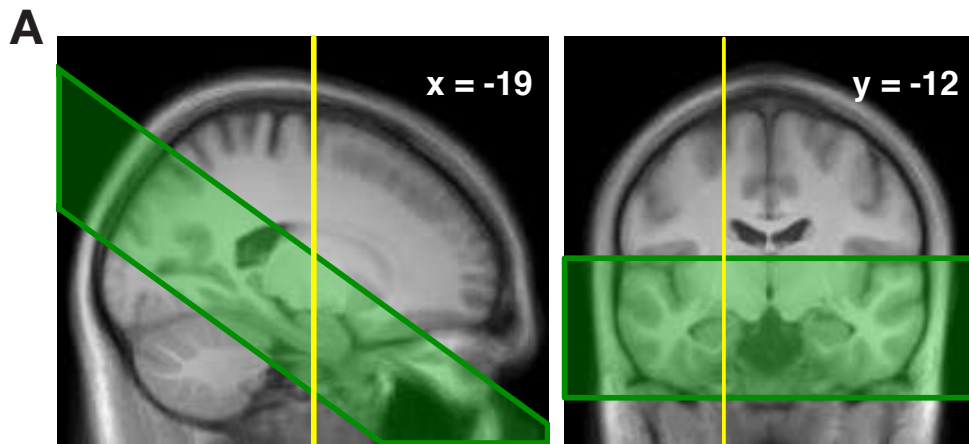


Figure 4

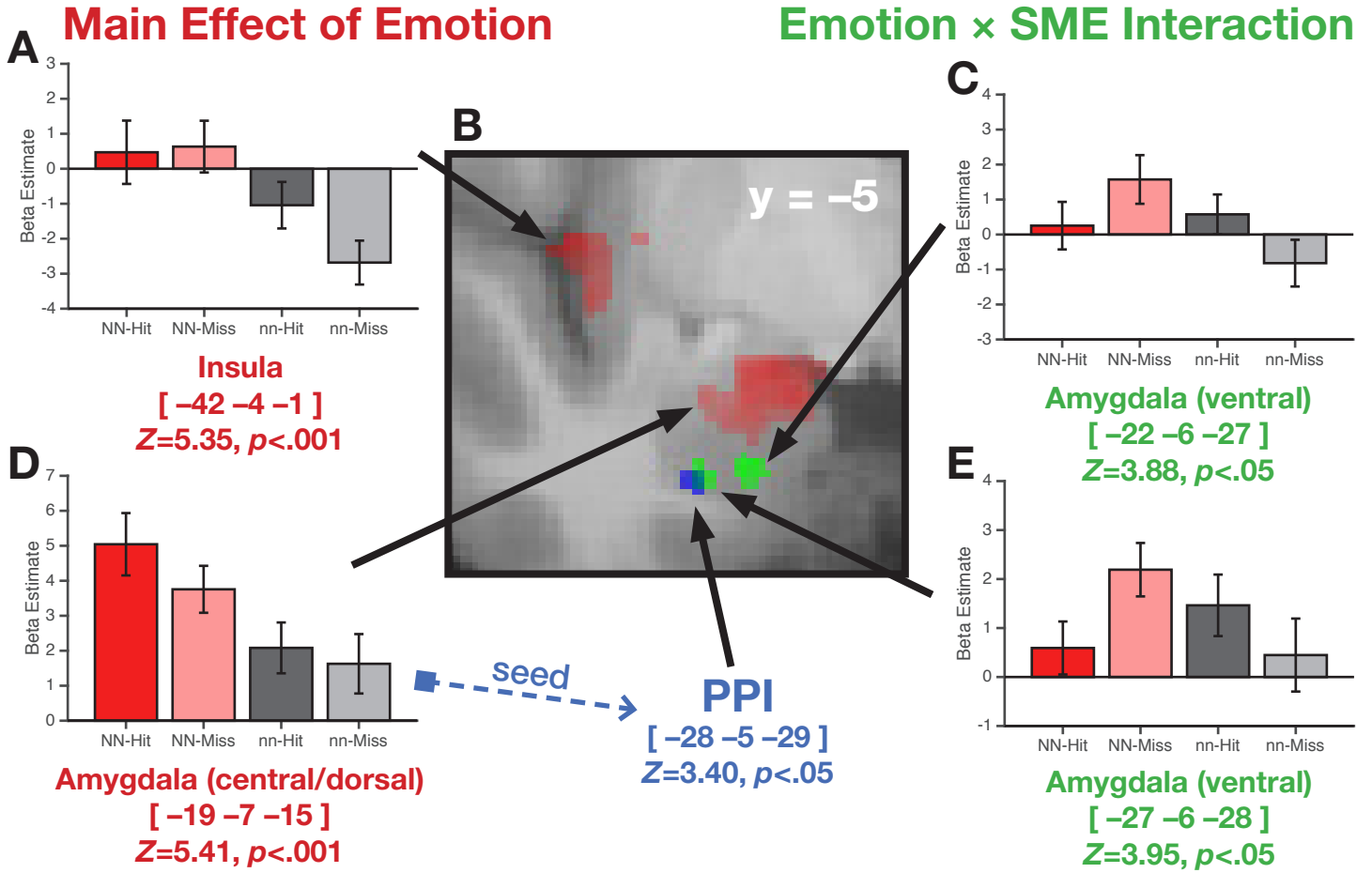


Figure 5

# Emotion × Subsequent Memory Effect Interaction

