

1 **Emotional arousal impairs association-memory:**
2 **Roles of prefrontal cortex regions**

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45 **Abstract**

46 The brain processes underlying impairing effects of emotional arousal on associative memory
47 were previously attributed to two dissociable routes using high-resolution fMRI of the MTL
48 (Madan et al. 2017): Extra-hippocampal MTL regions supporting associative encoding of neutral
49 pairs which suggested unitization; conversely, associative encoding of negative pairs involved
50 compensatory hippocampal activity. Here, whole-brain fMRI revealed prefrontal contributions:
51 dmPFC was more involved in hippocampal-dependent negative pair learning and vmPFC in
52 extrahippocampal neutral pair learning. Successful encoding of emotional memory associations
53 may require emotion regulation/conflict resolution (dmPFC), while neutral memory associations
54 may be accomplished by anchoring new information to prior knowledge (vmPFC).

55

56 **Article**

57 Emotional arousal is well known to enhance memory for individual items (Schümann and
58 Sommer 2018), but can have impairing effects on associative memory, particularly when items
59 cannot be easily unitized and inter-item associations have to be formed (Bisby and Burgess
60 2017; Murray and Kensinger 2013; Madan et al. 2012). The neural substrates of the impairing
61 effect of emotional arousal on associative memory have only begun to be explored (Madan et
62 al. 2017; Bisby et al. 2016). Emotional arousal may disrupt hippocampal functions that are
63 critical to promote binding and thereby lead to reduced associative memory for emotionally
64 arousing items ('disruption hypothesis') (Bisby et al. 2016). Conversely, encoding of neutral
65 items may engage extra-hippocampal medial temporal lobe (MTL) regions, areas we interpreted
66 to promote better incidental unitization of neutral than negative items, leading to a net-decrease
67 in associative memory for negative items ('bypassing hypothesis') (Madan et al. 2017).

68 Specifically, in our previous high-resolution fMRI study focussing on MTL regions
69 (Madan et al. 2017), extra-hippocampal MTL cortex was more active during encoding of neutral
70 than negative picture pairs, showed a subsequent memory effect (SME) for neutral picture pairs,
71 and neutral pair encoding was accompanied by more between-picture saccadic eye-movements
72 compared to negative pairs. In line with previous findings of extra-hippocampal MTL areas
73 involved in association memory formation of merged or unitized items (Quamme et al. 2007;
74 Giovanello et al. 2006; Diana et al. 2008; Delhaye et al. 2019), we interpreted our fMRI and eye-
75 movement findings to suggest better incidental unitization of neutral picture pairs than negative
76 pictures pairs. A behavioural follow-up study confirmed that unitization, i.e., imagining the two
77 pictures as one ('interactive imagery'), was indeed rated as higher for neutral than negative
78 pairs, and this advantage in interactive imagery was linked to better associative memory for
79 neutral pairs, lending further support to the bypassing hypothesis (Caplan et al. 2019).

80 What would prevent emotional pairs from being as easily merged as neutral pairs? We
81 observed that during negative pair encoding, each individual picture was fixated longer
82 compared to neutral pictures. These longer fixation durations for negative pictures were related
83 to greater activity during negative than neutral pair encoding in the dorsal amygdala (likely the
84 centromedial group; Hrybouski et al. 2016), an activation which was functionally coupled to the
85 more ventral amygdala (likely the lateral nucleus Hrybouski et al. 2016). This ventral amygdala
86 activation exhibited a subsequent forgetting effect specifically for negative pairs. Given that
87 emotional items attract more attention to themselves and are more likely processed as
88 individual items (Markovic et al. 2014; Mather et al. 2015), we conjectured that this may make
89 pairs of emotional items harder to unitize and to benefit from extra-hippocampal unitization-
90 related processes such as interactive imagery. Interestingly, the hippocampus revealed a
91 subsequent memory effect specifically for negative pairs in Madan et al. (2017). We concluded
92 that when sufficiently arousing information precludes extra-hippocampal unitization-based
93 encoding, an alternative, compensatory, and effortful relational hippocampus-dependent
94 encoding strategy may be used.

95 Both findings, extra-hippocampal MTL encoding for neutral pairs and compensatory
96 hippocampal encoding for negative pairs, raise the question of which cortical areas could be
97 involved in these two dissociable associative encoding processes. Conceivably, successful
98 associative encoding of negative information may require participants to evaluate the emotional
99 content, and regulate emotional arousal/conflict, functions primarily associated with dorso-
100 medial PFC regions (dmPFC; Dixon et al. 2017), the anterior cingulate cortex (ACC; Botvinick
101 2007), and posterior areas of the ventro-medial PFC (vmPFC; (Yang et al. 2020). To unitize
102 two pictures through interactive imagery, retrieval of semantic memories and prior knowledge
103 regarding the contents of the two pictures is likely helpful. Semantic memory processes have
104 been attributed to the left inferior frontal gyrus (left IFG; Binder and Desai 2011). The vmPFC
105 (more anterior portions) could also be involved, owing to its role in relating new information

106 during encoding to prior knowledge, i.e., a ‘unitization-like’ process (Gilboa and Marlatte 2017;
 107 Sommer 2017). Motivated by our previous discovery and interpretation of the two distinct
 108 encoding processes in the MTL (Madan et al. 2017), the potential contribution of these cortical
 109 areas in neutral and negative association memory was explored here by using a whole-brain
 110 scan and overcoming the limitations of our previous high-resolution fMRI sequence focused only
 111 on the MTL in Madan et al. (2017).

112 In the current study, we therefore acquired standard-resolution whole brain fMRI (3
 113 Tesla Siemens Trio scanner, 3-mm thickness TR 2.21 s; TE 30 ms) of 22 male participants
 114 during exactly the same task as in Madan et al. (2017). Only male participants were recruited
 115 because of known sex-dependent lateralization of amygdala activity (Cahill et al. 2004;
 116 Mackiewicz et al. 2006), limiting the conclusions of the current study to males. Eye-movements
 117 were assessed as a proxy for overt attention (EyeLink 1000, SR Research, 17 participants with
 118 usable eye-tracking data). In each of three encoding-retrieval cycles, 25 neutral and 25 negative
 119 picture pairs were intentionally encoded. Pictures (e.g., objects, scenes, humans, animals) were
 120 selected from the International Affective Picture System (Lang et al. 2008) and the internet, and
 121 confirmed to have different valence and arousal through independent raters (details in (Madan

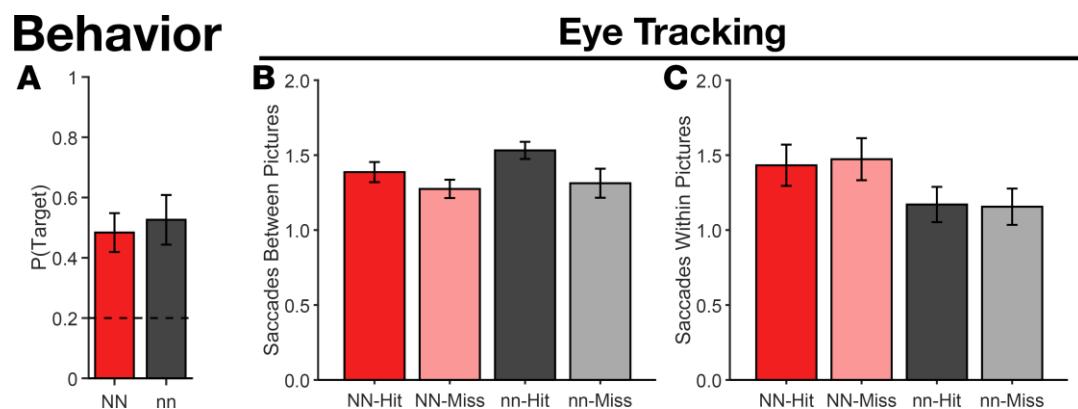


Figure 1: Behavioral and eye tracking results. (A) Accuracy in the associative recognition task (5-AFC) for all negative (NN) and neutral (nn) pairs. Chance level in the 5-AFC associative recognition task was $1/5 = 0.20$. (B) Mean number of saccades between the two pictures of a pair for remembered (Hit) and forgotten (Miss) negative (NN) and neutral (nn) pairs. (C) Mean number of saccades within pictures. Error bars are 95% confidence intervals around the mean, corrected for inter-individual differences (Loftus and Mason, 1994).

122 et al. 2017). Each encoding round was followed by a two-step memory test for each pair: In a
 123 Judgement of Memory (JoM) task one picture served as retrieval cue and volunteers indicated
 124 their memory (yes/now) for the other picture of the original pair. Then the same picture was
 125 centrally presented again, surrounded by five same-valence pictures (one correct target, four
 126 lures) in a 5-alternative forced-choice associative recognition test. Participants chose the target
 127 picture from the array with an MR-compatible joystick.

128 As in our previous studies, associative recognition was less accurate for negative (NN)
 129 ($M = .47$) than neutral (nn) pairs ($M = .51$; $t(22) = 2.49, p = .02$). Subjective memory confidence
 130 (JoM) for neutral pairs ($M = .41$) was not significantly different from confidence for negative pairs
 131 ($M = .43$; $t(22) = 1.19, p = .25$) (Figure 1A; Madan et al. 2017; Caplan et al. 2019).

132 Average fixation durations (a proxy for the depth of processing of individual pictures)
 133 was longer for negative than neutral pictures ($F(1,16) = 9.59, p = .007$), with no main effect of

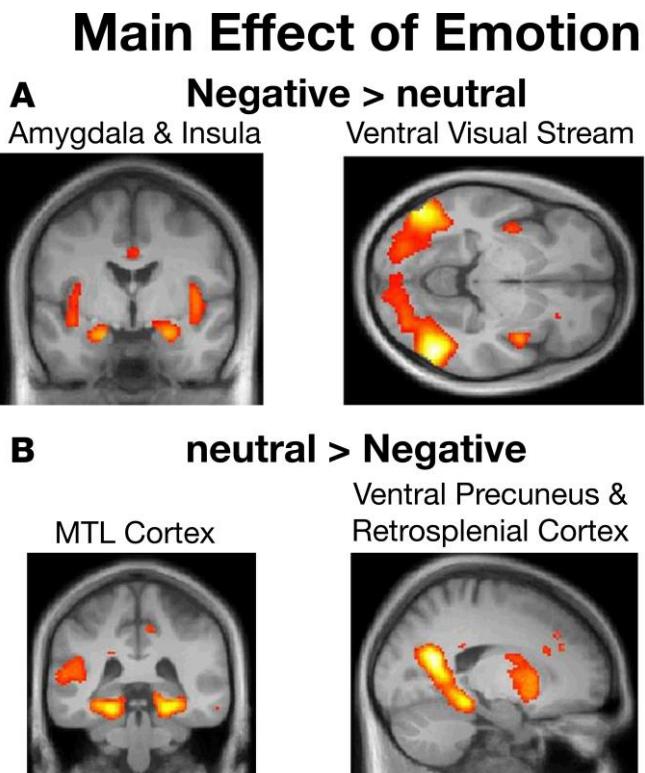


Figure 2: Main effects of emotion - fMRI results. (A) Greater activity during negative pair processing irrespective of subsequent memory success. (B) Greater activity during neutral than negative pairs processing. t-maps thresholded at $p < .001$ uncorrected for visualization purposes. t-value color coded.

134 memory ($F(1,16) = .11, p = .75$), nor emotion–memory interaction ($F(1,16) = 1.27, p = .28$). The
135 number of fixations was also higher for negative than neutral pictures ($F(1,16) = 5.56, p = .03$),
136 again with no main effect of memory ($F(1) = 1.56, p = .23$), nor interaction ($F(1,16) = .26, p = .61$).
137 The number of saccades within each picture (i.e., visual exploration within but not across items,
138 reflecting intra-item processing) was higher for negative than neutral pairs (Figure 1 B; $F(1,16) =$
139 33.38, $p < .001$), with no main effect of memory ($F(1,16) = .02, p = .89$) nor interaction ($F(1,16)$
140 = .15, $p = .71$). However, the number of saccades between the two pictures of a pair, which may
141 support associative processing, was substantially lower for negative than neutral pairs (Figure 1
142 C; $F(1,16) = 7.67, p = .01$). Importantly, there were more between-picture saccades for pairs that
143 were later remembered than forgotten, i.e., a subsequent memory effect based on between-
144 picture saccades ($F(1,16) = 8.43, p = .01$). This effect did not further interact with emotion
145 ($F(1,16) = 2.64, p = .12$). Thus, association-memory success was driven by inter-item saccades,
146 and these were reduced in negative trials. Participants spent more attention to individual
147 negative than neutral pictures (fixation duration and number of within-picture saccades), but this
148 was unrelated to association memory success.

149 The fMRI data were preprocessed (slice-timing corrected, realigned and unwarped,
150 normalized using DARTEL and smoothed, FWHM=8 mm) and analyzed using SPM12. First-
151 level models were created with four regressors that modeled the onsets of the 2 (negative and
152 neutral) x 2 (subsequent hits and misses) conditions of interest. Results of all fMRI analyses
153 were considered significant at $p < .05$, family-wise-error (FWE) corrected for multiple
154 comparisons across the entire scan volume or within the a priori anatomical regions of interest
155 (ROIs). ROIs for the hippocampus, amygdala and extra-hippocampal MTL were re-used from
156 our previous study (Madan et al. 2017). The prefrontal ROIs, i.e. dmPFC, ACC, vmPFC and left
157 inferior frontal gyrus ROIs, were manually traced on the mean T1 image using ITK-SNAP 3.6.0
158 (Yushkevich et al. 2006) following schematic drawings based on meta-analyses (Dixon et al.
159 2017; Gilboa and Marlatte 2017; Binder and Desai 2011).

160 The second level analyses based on the resulting individual beta-images and subject as
161 a random factor replicated a well-established network of brain areas involved in negative
162 emotion processing (Spalek et al. 2015): greater activity during processing negative than neutral
163 picture pairs in the amygdala, insula, right inferior frontal gyrus, mid and anterior cingulate
164 cortex as well as visual areas (Figure 2 A). As in our previous study, we correlated the
165 difference in left amygdala activity with the difference in eye movements for negative minus
166 neutral trials, showing a significant correlation with the number of within-picture saccades ($r =$
167 .50, $p = .018$). Thus, higher left amygdala activity was associated with increased visual search
168 *within* negative pictures. We conducted a psychophysiological interaction analysis (PPI) using
169 this amygdala region as seed and contrasted functional coupling during successful vs.
170 unsuccessful negative with successful vs. unsuccessful neutral pair encoding (i.e. the
171 interaction of valence and subsequent memory success). This PPI revealed stronger coupling
172 during successful encoding of negative compared to neutral pairs with a (non-significant) cluster
173 in the dmPFC ($Z = 3.01$, [-12 38 26]). Simple effects showed that the amygdala was more
174 strongly coupled with the dmPFC during successful than unsuccessful negative pair encoding (Z
175 = 3.63, [-2 16 42]).

176 Neutral pair processing was associated with greater activity than negative pair
177 processing in the bilateral extra-hippocampal MTL-cortex, ventral precuneus (vPC), retrosplenial
178 cortex (RSC), middle occipital gyrus and putamen (Figure 2 B). In addition, we observed a
179 general SME irrespective of valence in the left hippocampus ([-28 -16 -24], $Z = 3.49$, $p = .04$).

180 An interaction between pair valence and SME with greater neutral than negative SME
181 was observed in vmPFC (Figure 3 A), together with a (non-significant) cluster in right MTL-
182 cortex ([26 -24 -28], $Z = 3.16$, $p = 0.11$). We conducted a PPI using this vmPFC region as seed
183 and contrasted functional coupling during successful vs. unsuccessful neutral with successful
184 vs. unsuccessful negative pair encoding. This PPI revealed stronger coupling during successful

SMExEmotion Interactions and PPIs

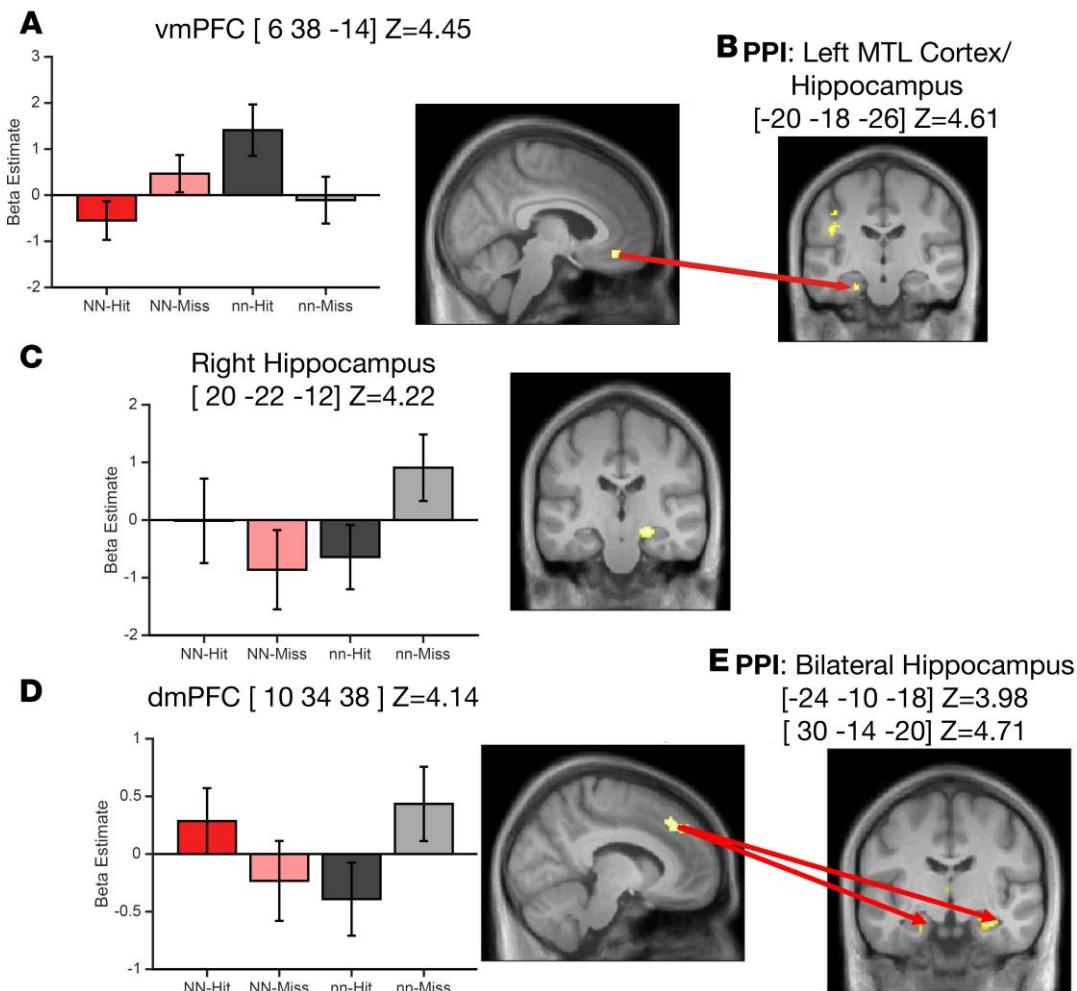


Figure 3: SME x Emotion interactions and PPIs (A) Activity in the vmPFC revealed a SME only for neutral but not negative pairs. (B) This region was stronger coupled during neutral than negative pair encoding with a cluster in the border of left MTL-cortex/hippocampus. (C, D) Activity in the right hippocampus and dmPFC revealed a SME only for negative pairs. (E) The dmPFC was stronger coupled during negative than neutral pairs encoding with the bilateral hippocampus. t-maps thresholded at $p < .001$ uncorrected for visualization purposes. Error bars are 95% confidence intervals around the mean, corrected for inter-individual differences (Loftus and Mason, 1994).

185 encoding of neutral compared to negative pairs in a cluster at the border of the extra-
186 hippocampal MTL-cortex reaching into the hippocampus ($[-20 -18 -26]$, $Z = 4.61$, Figure 3B).

187

188

189 Conversely, an interaction between pair valence and SME showing a greater negative-
190 than neutral SME was observed in the right hippocampal region (Figure 3 C), replicating our
191 previous finding of compensatory hippocampal encoding, and in the insula ($Z = 3.7$, [38 2 8]).

192 Within prefrontal cortex, the dorsal medial prefrontal cortex (dmPFC, $Z = 4.14$, Figure 3 D), also
193 showed this effect. Neutral pairs showed a subsequent forgetting effect, i.e., greater activity
194 during unsuccessful encoding of neutral pairs, in these regions (Figures 3 C/D).

195 Similar to the PPI with the vmPFC seed, we conducted a PPI with the dmPFC cluster as
196 seed. This PPI revealed the bilateral hippocampus to be more strongly coupled with the dmPFC
197 during successful negative than neutral pair encoding ($Z = 3.98$, [-24 -10 -18], $Z = 4.71$, [30 -14 -
198 29], Figure 3 E). The correlational analyses of activity in the dmPFC and vmPFC (valence ×
199 encoding success interactions) with the corresponding eye-tracking measures were non-
200 significant, possibly due to low reliability of difference measures (Schümann et al. 2019).

201 The current findings, first, replicated the impairing effects of emotional arousal on
202 association memory previously observed in six experiments across four studies (Madan et al.
203 2017; Caplan et al. 2019; Madan et al. 2012). We built on these previous findings here by
204 identifying cortical, especially prefrontal areas involved in the associative memory advantage for
205 neutral pairs and those involved in the compensatory mechanism for learning negative pairs. In
206 particular, vmPFC activity more strongly supported successful encoding of neutral than negative
207 pairs and during this process, showed stronger coupling with a cluster at the border between
208 MTL-cortex and hippocampus. Conversely, the dmPFC was more engaged and more strongly
209 coupled with the hippocampus during successful negative than neutral pair encoding.

210 We observed more and longer fixations, as well as more within-picture saccades for
211 individual negative pictures compared to neutral pictures, resembling previously reported eye-
212 movement findings (Bradley et al. 2011; Dietz et al. 2011). We had previously shown that
213 increased attention (fixation duration) to individual negative pictures is linked to centromedial
214 amygdala activity (not measurable here due to the whole-brain scan resolution), and functionally
215 coupled with a negative pair-specific subsequent forgetting effect in the lateral amygdala
216 (Madan et al. 2017). These findings together suggest that increased attention attracted by

217 individual negative pictures does not support associative memory, or may even be detrimental
218 (cf., Hockley and Cristi 1996).

219 The dmPFC contributed more to negative than neutral association memory and was
220 functionally coupled to the hippocampus, which complements our interpretation of possibly
221 compensatory activity in the hippocampus during negative pair encoding (Madan et al. 2017).
222 The amygdala on the other hand was stronger coupled with the dmPFC during successful
223 encoding of negative pairs which might reflect the detection of aversive stimuli by the amygdala.
224 The dmPFC not only plays a role in emotion regulation (Dixon et al. 2017; Ochsner et al. 2012;
225 Wager et al. 2008; Kohn et al. 2014); it is the central node in the cognitive control network. In
226 particular, the dmPFC regulates conflicts between goals and distracting stimuli by boosting
227 attention towards the relevant task (Weissman 2004; Iannaccone et al. 2015; Ebitz and Platt
228 2015; Grinband et al. 2011). Consistent with this role in the current task, the dmPFC was
229 functionally more strongly coupled with the bilateral hippocampus during successful negative
230 compared to neutral pair learning. The involvement of the dmPFC during successful negative
231 (but unsuccessful neutral, discussed below) pair encoding may suggest that it resolves conflicts
232 between the pre-potent attention to the individual negative pictures and the current task goals,
233 i.e., their intentional associative encoding. One way to do so might involve the dmPFC's role to
234 regulate the negative emotions elicited by the pictures in order to focus on the associative
235 memory task.

236 Neutral pairs elicited more between-picture saccades than negative pairs, as in (Madan
237 et al. 2017). The vmPFC was more strongly involved in successful associative encoding of
238 neutral than negative pairs and more strongly coupled with the extra-hippocampal MTL cortex
239 bordering the hippocampus during successful neutral compared to negative pair encoding.
240 Anterior vmPFC regions and their coupling with the MTL have been implicated in retrieval of
241 consolidated memories and in anchoring new information to prior knowledge (Sommer 2017;
242 van Kesteren et al. 2013; Brod and Shing 2018; Schlichting and Preston 2015; Gilboa and

243 Marlatte 2017; Nieuwenhuis and Takashima 2011; Sekeres et al. 2018). We previously
244 observed that interactive imagery (forming one instead of two images to memorize) was higher
245 for neutral than negative pairs (Caplan et al. 2019), perhaps reflected by the increased
246 between-picture saccades in the current study. Assuming that the anterior vmPFC subserves
247 retrieval of prior knowledge, its engagement during successful neutral pair encoding may have
248 supported such incidental unitization processes here as well. Negative pictures are inherently
249 semantically more related (Barnacle et al. 2016), which implies that they may share even more
250 prior knowledge than neutral pictures. However, the retrieval of this prior knowledge may be
251 inhibited by the attraction of attention to *individual* negative pictures, not their arbitrary pairing as
252 in the current task. Incidental unitization can occur through rather subtle manipulations (Ford et
253 al. 2010; Giovanello et al. 2006; Diana et al. 2008; Bader et al. 2010; Li et al. 2019) or even
254 entirely without any instruction, for example, when the items' combination is itself meaningful or
255 familiar (Ahmad and Hockley 2014). We suggest that similar incidental unitization processes
256 may have occurred here as well. Memory for unitized associations is independent of
257 hippocampal memory processes and can be based solely on the extra-hippocampal MTL
258 (Quamme et al. 2007; Haskins et al. 2008; Staresina and Davachi 2010). Our previous high-
259 resolution fMRI study supported such a bypassing hypothesis, i.e., extra-hippocampal MTL-
260 cortex involvement in the successful associative encoding of neutral but not negative pairs
261 (Madan et al. 2017). Here, this interaction did not reach significance in the MTL-cortex, but the
262 p-value of 0.11 can be considered suggestive based on our strong a priori-hypothesis. Notably,
263 in our previous study using a scanning resolution of 1 mm³ the cluster included only 17 voxels,
264 which would correspond to <1 voxel here. Therefore, we assume the lower sensitivity here was
265 due to the lower spatial resolution.

266 Unexpectedly, we observed greater activity during unsuccessful encoding of neutral
267 pairs in the same regions that promoted successful encoding of negative pairs, i.e., the dmPFC
268 and hippocampal region. Hockley et al. (2016) previously observed that incidental but not

269 intentional encoding of associations (for word pairs) improved for items with stronger pre-
270 experimental associations. Perhaps using an effortful (dmPFC/hippocampal) learning strategy
271 for neutral pairs, i.e., pairs that are already more likely incidentally linked or linkable (e.g.,
272 through interactive imagery) may not have helped encoding. The forgotten neutral pairs
273 underlying the SFE in these regions may then have been simply the hardest-to-learn neutral
274 pairs, i.e., pairs where both encoding strategies failed. Evidently, future studies should test such
275 speculations directly.

276 Our interpretation of the dmPFC and vmPFC as signifying in emotion regulation and
277 unitization in this task was based on previous studies. Evidently, because we did not manipulate
278 unitization and/or emotional regulation, these processes remain hypothetical. However, within
279 this framework, we addressed two hypotheses regarding interactions between
280 hippocampal/extrahippocampal MTL regions and prefrontal cortex during association memory
281 formation. The disruption hypothesis proposes that the hippocampus is equally responsible for
282 encoding of negative and neutral association memory but that for negative memories,
283 hippocampal activity is inhibited by the amygdala via the prefrontal cortex (Bisby et al. 2016;
284 Murray and Kensinger 2013). The vmPFC has known involvement in negative emotion
285 processing (Yang et al. 2020), and the observed activity pattern in the vmPFC could appear to
286 disrupt hippocampal association memory processes for negative pairs. However, according to
287 the bypassing hypothesis (Madan et al. 2017), successful encoding of negative (compared to
288 neutral) pairs requires the hippocampus since fewer extrahippocampal contributions are
289 available. Supporting the bypassing hypothesis, we observed that the vmPFC was negatively
290 functionally coupled with extrahippocampal MTL-cortex (bordering the hippocampus),
291 suggesting that the vmPFC decreased extra-hippocampal contributions to association memory
292 for negative pairs. The bypassing hypothesis is also supported by our finding that the
293 hippocampus was not less but *more* involved in negative compared to neutral pair encoding,

294 i.e., we observed no evidence for a prefrontally (e.g., vmPFC)-mediated disruption of
295 hippocampal activity by emotion.

296 In conclusion, the two critical prefrontal cortex regions linked to MTL memory processes
297 in the current study were the dmPFC, involved in successful hippocampal-dependent negative
298 pair learning and the vmPFC, supporting successful neutral pair learning that relied on extra-
299 hippocampal MTL involvement.

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