

1 Hippocampal mechanisms support 2 cortisol-induced memory enhancements

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8

9 **Abstract** Stress can powerfully influence episodic memory, often enhancing memory encoding for
10 emotionally salient information. These stress-induced memory enhancements stand at odds with
11 demonstrations that stress and the stress-related hormone cortisol can negatively affect the
12 hippocampus, a brain region important for episodic memory encoding. To resolve this apparent conflict
13 and determine whether and how the hippocampus supports memory encoding under cortisol, we
14 combined behavioral assays of associative memory, high-resolution functional magnetic resonance
15 imaging (fMRI), and pharmacological manipulation of cortisol in a within-participant, double-blinded
16 procedure. Hydrocortisone led to enhanced functional connectivity between hippocampal subregions,
17 which predicted subsequent memory enhancements for emotional information. Cortisol also modified
18 the relationship between hippocampal representations and memory: whereas hippocampal signatures of
19 distinctiveness predicted memory under placebo, relative integration predicted memory under cortisol.
20 Together, these data provide novel evidence that the human hippocampus contains the necessary
21 machinery to support emotional memory enhancements under stress.

22 **keywords:** emotional memory, associative memory, stress, cortisol, functional connectivity, pattern
23 similarity

24

25 Introduction

26 Our daily lives are filled with stressful events, from working up against a deadline to hearing that a loved
27 one is ill. Such stressful events can transform the way we encode experiences into memory: Stress can im-
28 pair memory for neutral, non-stress relevant information (e.g., a conversation with a friend while you were
29 worrying about work), yet enhance memory for emotionally salient or stress-relevant experiences (e.g., a
30 conversation with a family member about their illness) (*Joëls et al., 2006; McGaugh et al., 2015; Shields*
31 *et al., 2017; Goldfarb, 2019*). Indeed, acute stress can powerfully enhance emotionally salient memories
32 (*Payne et al., 2006, 2007; Smeets et al., 2007; Zoladz et al., 2011; Shields et al., 2022*) and elevated levels of
33 stress-related hormones such as glucocorticoids are associated with enhanced emotional memory in both
34 rodents (*Okuda et al., 2004; Roozendaal et al., 2006; Shors, 2006; Sandi and Pinelo-Nava, 2007*) and humans
35 (*Buchanan and Lovallo, 2001; Abercrombie et al., 2003, 2006; Kuhlmann and Wolf, 2006; Schwabe et al.,*
36 *2008; Segal et al., 2014*). However, pinpointing the neural mechanisms underlying this selective strengthen-
37 ing of emotional memories under stress presents a puzzle.

38 Here we focus on the hippocampus, a key region for arbitrating stress effects on memory. The hip-
39 pocampus plays a critical role in episodic memory by rapidly binding diverse elements of an experience
40 into a detailed, holistic associative memory representation (*Davachi, 2006*). The hippocampus is also highly
41 sensitive to stress, in part because of its high density of glucocorticoid receptors (*Seckl et al., 1991; Lupien*

42 *et al., 2007; Wang et al., 2013*). Such stress effects are often deleterious: In nonhuman animal models,
43 glucocorticoids tend to impair hippocampal long-term potentiation (LTP), are associated with atrophy of
44 hippocampal neurons, and have been linked to decreased hippocampal neurogenesis (*Kim and Diamond,*
45 **2002**). In humans, direct administration of glucocorticoids via hydrocortisone reduces hippocampal BOLD
46 activity (*Pruessner et al., 2008; Lovallo et al., 2010; Bini et al., 2022*). Accordingly, negative stress effects
47 on the hippocampus have been instrumental in explaining stress-induced episodic memory impairments
48 (*McEwen and Sapolsky, 1995; Kim and Diamond, 2002*). Yet, as discussed earlier, stress can also *enhance*
49 memory, including promoting the very types of episodic memory that are thought to be supported by the
50 hippocampus (*van Ast et al., 2014; Goldfarb et al., 2019*). How could stress enhance emotional episodic
51 memories while impairing the function of the brain region important for episodic memory?

52 One possibility is that stress alters the underlying neural mechanisms of memory encoding, such that
53 memories enhanced under stress rely on extrahippocampal mechanisms. For example, whereas the hip-
54 pocampus often shows greater BOLD activity for subsequently remembered (versus forgotten) associations
55 (*Davachi et al., 2003*), stress can attenuate (*Qin et al., 2012*) or reverse (*Henckens et al., 2009*) this effect.
56 Stress also alters the electrophysiological signatures of memory encoding (*Meier et al., 2020*). Such findings
57 have been taken as evidence that stress biases memory encoding away from the hippocampus and towards
58 cortical regions, perhaps explaining why memories encoded under stress are less detailed, or more gist-like
59 (*Qin et al., 2012; Pedraza et al., 2016*). Glucocorticoids and stress also broadly influence the neural systems
60 that support memory (*Segal et al., 2010; Hermans et al., 2014; Goldfarb and Phelps, 2017; Schwabe et al.,*
61 **2022**). Many emotional memory enhancements under stress have been explained by enhanced amygdala
62 activity (*Roosendaal et al., 2009*), as well as hippocampal-amygdala interactions (*Roosendaal and McGaugh,*
63 **1997; Kim et al., 2001; Ghosh et al., 2013; Vaisvaser et al., 2013; de Voogd et al., 2017**).

64 Another possibility is that stress acts directly on hippocampal learning pathways to enhance later mem-
65 ory. Although we mentioned above that glucocorticoids can impair hippocampal LTP, there is also abun-
66 dant and opposite evidence that they can enhance hippocampal LTP (*Rey et al., 1994; Pavlides et al., 1995;*
67 *Krugers et al., 2005; Karst and Joëls, 2005; Karst et al., 2005; Vandael et al., 2021*). Such benefits are par-
68 ticularly apparent when stress occurs at the time of synaptic stimulation (i.e., encoding) (*Joëls et al., 2006;*
69 *Wiegert et al., 2006*). This facilitation is consistent with the role of the hippocampus in regulating stress re-
70 sponses; if stress fully blocked hippocampal function, such regulation would be impossible (*Ulrich-Lai and*
71 *Herman, 2009*). In humans, cortisol effects on hippocampal BOLD activity have been mixed (*Harrewijn et al.,*
72 **2020**); in addition to findings of decreased activity, there is also evidence for increased hippocampal BOLD
73 following hydrocortisone (*Symonds et al., 2012*). Additionally, during an acute stress provocation, higher
74 cortisol responses tracked greater hippocampal BOLD increases (*Sinha et al., 2016*). Emotional memory
75 enhancements under stress have also been linked to increased memory-related oscillations in the medial
76 temporal lobe (*Heinbockel et al., 2021*). Together, these data suggest that there may be intra-hippocampal
77 mechanisms to account for emotional memory enhancements with glucocorticoids.

78 Here we combine high-resolution fMRI, behavioral measures, and double-blind hydrocortisone admin-
79 istration to probe the hippocampal mechanisms underlying memory encoding under cortisol. By using
80 high-resolution fMRI, we embrace the heterogeneity of the hippocampus by examining responses and con-
81 nectivity profiles of different subfields (e.g., CA1 and a combined CA2/3/dentate gyrus [DG] region). This is a
82 critical advance as nonhuman animal findings demonstrate distinct stress effects across subfields (*Sharvit*
83 *et al., 2015; Alkadhi, 2019*) and human research indicates that subfields support distinct aspects of mem-
84 ory (*Schapiro et al., 2017; Duncan and Schlichting, 2018*), with CA3 and DG supporting the computations
85 necessary for episodic memory (*Bakker et al., 2008; Molitor et al., 2021; Wanja et al., 2021; Wammes*
86 *et al., 2022*). During the fMRI scan, participants encoded emotional and neutral object-scene associations;
87 they then returned to the lab 24h later for memory tests (Figure 1). The emotional objects consisted of
88 alcoholic beverages that generally have positive valence and have been used in prior studies (*Goldfarb*
89 *et al., 2020*). Participants completed this procedure twice, once receiving 20mg hydrocortisone and once
90 receiving placebo prior to encoding (double-blinded; order counter-balanced). By examining how cortisol
91 influences behavioral measures of memory, neural signatures of encoding within the hippocampus, and
92 brain-behavior relationships, we identify novel mechanisms by which glucocorticoids modulate hippocam-

93 pal function to enhance emotional memory.

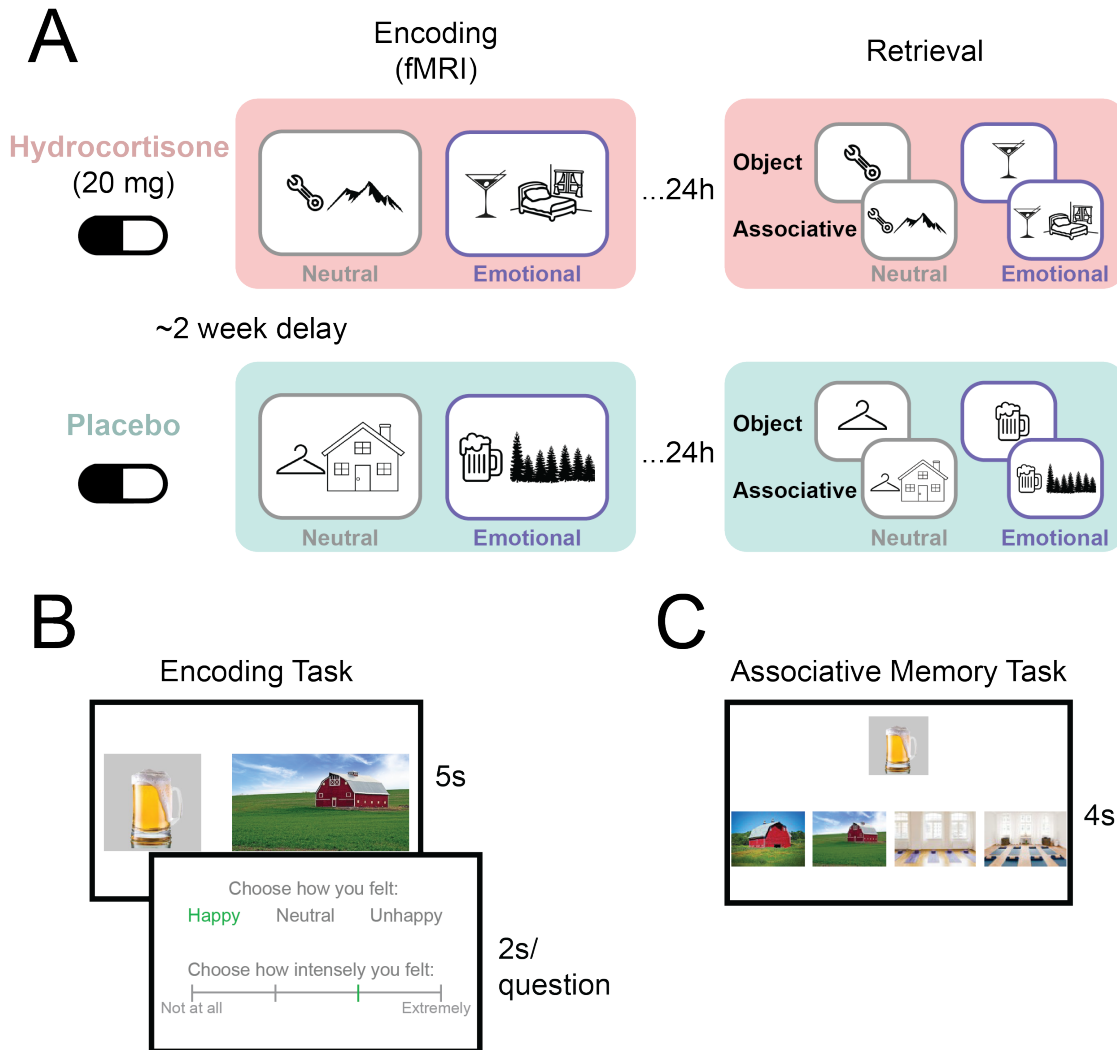


Figure 1. Task design. A) Participants completed the experimental procedure twice (on two separate weeks). They first received a pill containing either 20mg hydrocortisone or no active substance (placebo). They then completed a memory encoding task while undergoing fMRI. The encoding task consisted of two runs of encoding object-scene pair associations. Objects were either neutral (handheld objects) or emotionally salient (alcoholic beverages). Participants returned 24h later to be tested on their memory for individual objects and object-scene associations. B) During encoding, participants viewed an object-scene pair for 5s, during which they imagined the object and scene interacting. They then rated whether the imagined interaction made them feel happy, neutral, or unhappy (valence) and how intensely they felt that way (arousal). C) During the associative memory task, participants were shown an object and asked to identify its associated scene. The options included the correct scene, a perceptually matched lure scene, another scene (which had been encoded with a different object), and a perceptually matched lure for the incorrect scene. Choosing the correct scene denotes correct associative memory.

94 Results

95 Hydrocortisone administration leads to elevated cortisol, but no detectable changes in 96 affect or awareness

97 To validate the hydrocortisone tablet administration, we collected salivary samples throughout the session
98 (Supplemental Figure S1). Indeed, participants exhibited elevated salivary cortisol following drug, but not

99 placebo; drug-induced cortisol elevation was evident throughout encoding (pre- and post-encoding follow-
100 ing hydrocortisone relative to placebo: $p_s < 0.001$).

101 Despite this robust increase in peripheral cortisol, we did not observe significant changes in awareness
102 or overall affect (PANAS, measured pre- and post-scan; *Watson et al., 1988*). Overall, participants were
103 unaware of which pill they had received (immediately post-pill: 9.4% correct, 74% unsure; post-scan: 29%
104 correct, 45% unsure). Furthermore, we found no significant changes in positive [$F(1, 23) = 0.81, p = 0.38$] or
105 negative [$F(1, 23) = 1.39, p = 0.25$] affect.

106 **Hydrocortisone modulates subjective affect at encoding**

107 After pill administration, participants completed two runs of an associative memory encoding task while
108 undergoing fMRI (Figure 1A, left). To examine effects of hydrocortisone on emotional memory, each run
109 involved either emotionally salient or neutral trials. One run consisted of forming trial-unique associations
110 between neutral, handheld household objects (e.g., a wrench) and neutral scenes; the other run consisted of
111 associations between an emotionally salient, alcoholic beverages (e.g., a martini) and scenes (more details
112 on stimuli in Methods: Task Stimuli). Participants were instructed to vividly imagine each object and scene
113 interacting and then rate whether the imagined interaction was happy, neutral, or unhappy (valence rating)
114 and how intensely they felt that way (arousal rating; Figure 1B).

115 Hydrocortisone did not influence arousal ratings, $F(1, 75) = 0.37, p = 0.54$. There was a main effect of
116 trial type (emotionally salient vs. neutral) [$F(1, 75) = 6.27, p = 0.015$], though this did not interact with pill
117 [$F(1, 75) = 0.64, p = 0.43$]. Thus, consistent with the stimulus design, participants rated emotionally salient
118 associations as more arousing than the neutral associations (Figure 2A), and this was not modulated by
119 hydrocortisone.

120 In contrast, hydrocortisone did modulate valence ratings (Figure 2B). There was a main effect of valence
121 on ratings [$F(2, 279) = 95.11, p < 0.001$], such that the majority of trials were rated as neutral. There was
122 no main effect of stimulus type [$F(1, 279) = 0.042, p = 0.84$], nor did trial type reliably interact with valence
123 [$F(2, 279) = 2.49, p = 0.085$]. Although there was no main effect of pill [$F(1, 279) = 0.062, p = 0.80$], there was a
124 valence by pill interaction [$F(2, 279) = 3.53, p = 0.031$]. This interaction was driven by a smaller proportion of
125 trials rated as “neutral” under hydrocortisone, relative to placebo ($\beta = -0.082[SE = 0.036], t(279) = -2.28, p =$
126 0.023). That is, hydrocortisone amplified emotional salience at encoding by shifting participants’ valence
127 ratings away from neutral and towards feeling more positive or negative about the encoded associations.

128 **Hydrocortisone alters the relationship between arousal and memory encoding**

129 Participants were tested on their memory for encoded associations 24h later. On each trial, participants
130 viewed an object and were asked to select which of four scenes was paired with the object at encoding
131 (Figure 1C). Participants selected the correctly paired scene more often than chance (chance = 0.25; mean
132 proportion correct = 0.36, SD = 0.094). Performance did not differ as a function of pill [$F(1, 75) = 0.25, p =$
133 0.62], though it did differ by trial type [$F(1, 75) = 8.23, p = 0.0054$], with better memory for neutral associations
134 (Figure 2C).

135 Prior work has demonstrated that subjective affect can modulate memory effects under cortisol (*Aber-*
136 *crombie et al., 2003*). Thus, we examined whether memory was affected by subjective arousal differently
137 under hydrocortisone vs. placebo. Indeed, arousal and pill interacted [$F(1, 71) = 9.30, p = 0.0032$], such
138 that participants with higher subjective arousal had better associative memory under hydrocortisone, but
139 worse associative memory under placebo (Figure 2D). This difference was significant for both emotional
140 [$\beta = 0.080[0.40], t(71) = 2.01, p = 0.048$] and neutral [$\beta = 0.095[0.038], t(71) = 2.48, p = 0.016$] trial types.

141 As hydrocortisone modulated valence ratings during encoding, we asked whether the shifts towards
142 happy or unhappy judgments were related to later memory. Indeed, the change in subjective “happy”
143 ratings predicted the change in associative memory from placebo to hydrocortisone across participants,
144 [$F(1, 23) = 6.22, p = 0.020$], with more “happy” ratings under hydrocortisone corresponding to better mem-
145 ory (Figure 2E). This effect did not interact with trial type [$F(1, 23) = 0.0070, p = 0.93$] and was specific to
146 positive valence. That is, the change in “unhappy” ratings did not predict differences in memory for either
147 trial type across participants [$F(1, 23) = 0.36, p = 0.56$].

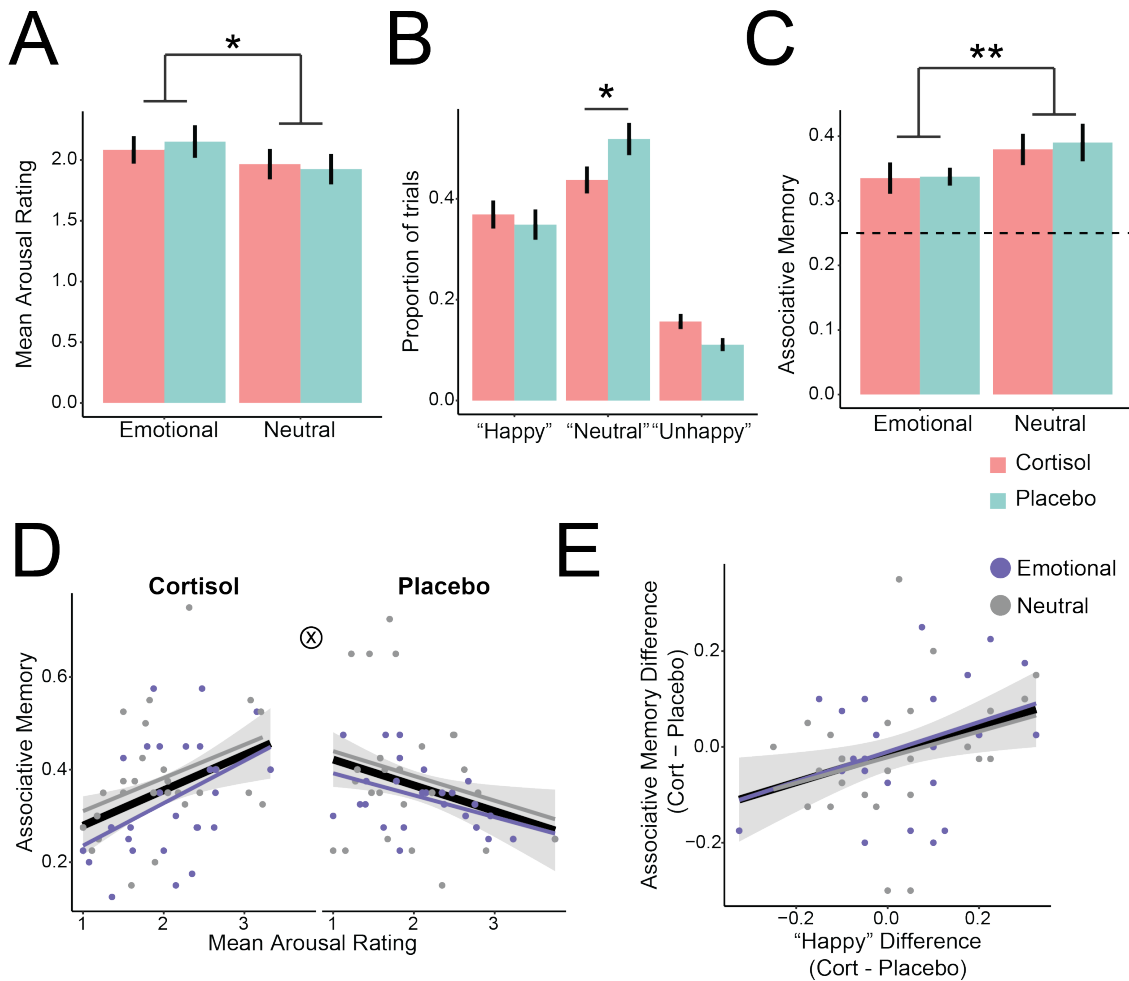


Figure 2. Behavioral Results. A) Participants rated emotionally salient associations as more arousing than neutral associations. B) Cortisol altered the valence of encoded associations, such that participants were less likely to endorse feeling “neutral” about the object-scene pair. C) Participants performed above chance (.25; dashed line) on the associative memory test, with better memory for neutral associations. D) Cortisol altered the relationship between arousal and memory. Participants with high subjective arousal had better associative memories under cortisol, but worse memories under placebo. E) The cortisol-induced change in happiness ratings predicted associative memory, such that participants with greater increases in happiness had better memory. A-C: Error bars denote standard error of the mean across participants; D-E: Error shading indicates 95% confidence interval around the line of best fit, collapsed across trial types (black line). Individual colored lines indicate the line of best fit within each trial type. * $p < 0.05$; ** $p < 0.01$

148 Together, these data demonstrate that subjective affect modulates hydrocortisone effects on encoding.
 149 Subjective arousal and positive affect bolstered memories encoded with elevated cortisol, but impaired
 150 memories under placebo. Although our primary analyses focused on associative memory for object-scene
 151 pairs, we observed similar patterns for item recognition of individual objects (Supplemental Figure S2).

152 Hydrocortisone enhances intra-hippocampal connectivity to promote emotional memory

153 After establishing that hydrocortisone interacts with subjective arousal to promote memory, we next sought
 154 to investigate whether hippocampal mechanisms could support these memory enhancements. We first
 155 examined whether intra-hippocampal connectivity was modulated by hydrocortisone. The hippocampus
 156 contains multiple subfields connected to entorhinal cortex (EC), the primary input/output region for the
 157 hippocampus (Figure 3A, left). Information from EC is relayed to CA3/DG, which then connects to CA1; CA1

158 then communicates back out to EC (Figure 3A, right). This circuit (known as the trisynaptic pathway) is
159 particularly important for episodic memory encoding given the sparse connections and high inhibition in
160 CA3 and DG that enable pattern separation (*Schapiro et al., 2017*). We performed a background connectiv-
161 ity analysis (*Al-Aidroos et al., 2012*) to examine how BOLD responses throughout the hippocampal circuit
162 co-fluctuate during encoding following hydrocortisone. Although we ran this analysis for all edges of our
163 simplified hippocampus circuit (EC-CA23DG, CA1-CA23DG, and CA1-EC), we were particularly interested in
164 the CA1-CA23DG edge, as this directly probes hydrocortisone effects on the hippocampus.

165 Hydrocortisone enhanced connectivity between CA1 and CA23DG [$F(1, 72) = 5.20, p = 0.026$]. Although
166 this effect was only reliable for CA1-CA23DG, it was numerically present for both EC-CA23DG [$F(1, 72) =$
167 $2.01, p = 0.16$] and EC-CA1 [$F(1, 72) = 2.38, p = 0.13$] as well; (Figure 3B)]. Connectivity did not differ between
168 trial types for any of the edges (main effect and cortisol interaction: $p_s > 0.40$). These data suggest that
169 cortisol promotes enhanced communication among hippocampal subfields.

170 Because prior work has suggested that stress can alter hippocampal-amygdala connectivity (e.g., *Vais-*
171 *vasser et al., 2013*), we next examined whether cortisol altered connectivity between the amygdala and the
172 hippocampal circuit (Supplemental Figure S3). Hydrocortisone was associated with a marginal decrease in
173 amygdala-EC connectivity [$F(1, 72) = 3.03, p = 0.086$], but had no effect on amygdala-CA1 [$F(1, 72) = 2.21, p =$
174 0.14] or amygdala-CA23DG connectivity [$F(1, 72) = 0.41, p = 0.53$]. As with intra-hippocampal connectivity,
175 amygdala-hippocampal connectivity did not differ between trial types (main effect and cortisol interaction:
176 $p_s > 0.30$). Together, these data suggest a specific role for hydrocortisone in enhancing intra-hippocampal
177 connectivity.

178 Given that intra-hippocampal, but not amygdala-hippocampal, connectivity was modulated by hydrocort-
179 isone, we next tested how intra-hippocampal connectivity related to subsequent associative memory. We
180 observed a three-way interaction between CA1-CA23DG connectivity, trial type, and pill, $F(1, 68) = 4.92, p =$
181 0.030 (Figure 3C). Under placebo, greater intrahippocampal connectivity was associated with stronger mem-
182 ory, and this did not differ between trial types [$\beta = -0.16[0.15], t(68) = -1.05, p = 0.30$]. However, following
183 hydrocortisone, greater connectivity positively predicted better memory for emotional, but not neutral as-
184 sociations (emotional vs neutral: $\beta = 0.28[0.13], t(68) = 2.14, p = 0.036$).

185 This finding suggests a reprioritization of hippocampal connectivity to promote emotional, rather than
186 neutral, memories under hydrocortisone. To probe whether this relationship was driven by emotionality,
187 we exploited the positive behavioral relationship between subjective arousal and associative memory with
188 hydrocortisone and assessed whether hippocampal connectivity under hydrocortisone also tracked sub-
189 jective arousal. Indeed, we observed a significant interaction between connectivity and trial type under
190 hydrocortisone, $F(1, 23) = 6.54, p = 0.018$. Mirroring the relationship between connectivity and associa-
191 tive memory, hippocampal connectivity positively tracked arousal for emotional, but not neutral, associa-
192 tions. In contrast, subjective arousal was not related to connectivity under placebo ($p_s > 0.50$), although we
193 note that the three-way interaction between connectivity, trial type, and pill was not statistically significant
194 [$F(1, 68) = 2.03, p = 0.16$].

195 We next exploited the behavioral relationship between associative memory and subjective valence, wherein
196 hydrocortisone-induced shifts in positive affect related to better associative memory. We probed the rela-
197 tionship between intra-hippocampal connectivity and subjective valence. We again computed difference
198 scores to assess whether hydrocortisone-associated changes in connectivity related to changes in valence
199 ratings. For positive affect, the difference in CA1-CA23DG connectivity marginally interacted with trial type
200 [$F(1, 22) = 4.25, p = 0.051$], such that connectivity changes positively predicted the change in “happy” rat-
201 ings for emotional, but not neutral trials (Figure 3E). This interaction was not present for negative affect
202 [“unhappy” ratings, $F(1, 22) = 0.97, p = 0.34$].

203 Together, these data suggest an intra-hippocampal mechanism supporting cortisol-induced enhance-
204 ment of emotional memories. Under placebo, CA1-CA23DG connectivity predicted episodic memory for
205 neutral stimuli, but this relationship shifted with hydrocortisone, with CA1-CA23DG connectivity selectively
206 predicting emotional memory. CA1-CA23DG connectivity also tracked aspects of subjective affect that mod-
207 ulate hydrocortisone effects on associative memory, thereby providing an intra-hippocampal explanation
208 for positive effects of hydrocortisone on emotionally arousing, positively valenced memories.

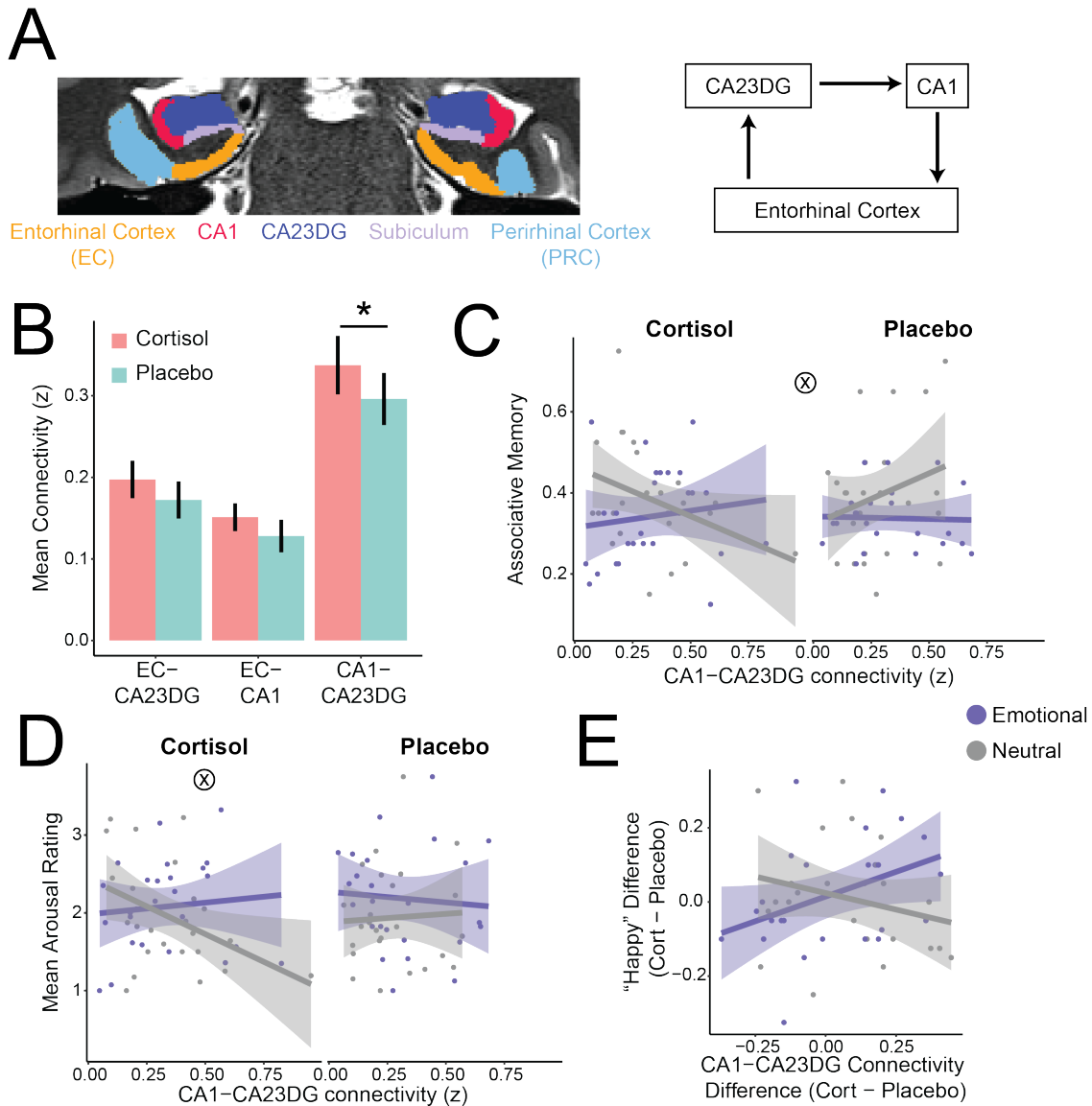


Figure 3. Background Connectivity Results. A) Left: example hippocampal and medial temporal lobe subfields on a representative participant; Right: schematic of hippocampal trisynaptic pathway. B) Hydrocortisone led to increased background connectivity through the hippocampal circuit. C) CA1-CA23DG connectivity interacted with pill and trial type to predict associative memory. D) CA1-CA23DG connectivity interacted with pill to predict subjective arousal. E) The cortisol-induced increase in happiness ratings as a function of the cortisol-induced increase in CA1-CA23DG connectivity. B: Error bars indicates standard error of the mean across participants; *p < 0.05. C-E: Error shading indicates 95% confidence interval around the best fit line.

209 **Hydrocortisone reverses the relationship between hippocampal pattern similarity and**
210 **memory**

211 The connectivity approach allowed us to examine how hydrocortisone modulates co-fluctuations in uni-
212 variate activity between hippocampal subregions. However, the representational content housed in those
213 subregions remains unclear. Prior work using multivariate pattern analysis of hippocampal activity demon-
214 strated that representational distinctiveness, particularly in CA23DG, supports episodic memory encoding
215 (*LaRocque et al., 2013; Wanjia et al., 2021*). This dissimilarity is computationally important, as minimizing
216 overlap between neural patterns associated with similar memories allows those memories to be encoded
217 distinctly, without interference from one another (*Favila et al., 2016; Chanales et al., 2017*). Thus, we next

218 explored the effects of hydrocortisone on representations within these hippocampal subfields during en-
219 coding, and how the similarity of these representations relates to memory. We examined within-run pattern
220 similarity, a metric of how similar the hippocampal pattern for an encoded association is to all other asso-
221 ciations within that run (Figure 4A).

222 Hydrocortisone did not affect within-run pattern similarity in either CA1 [$F(1, 72) = 1.21, p = 0.27$] or
223 CA23DG [$F(1, 72) = 0.36, p = 0.55$]. However, trial type did modulate CA23DG similarity [$F(1, 72) = 4.86, p =$
224 0.031], with relatively greater pattern similarity for emotional, relative to neutral associations (Figure 4B).
225 To ensure that this difference was not due to visual content (i.e., greater inherent visual similarity among
226 emotional objects), we also examined pattern similarity in lateral occipital cortex (LOC), an object-sensitive
227 visual region. There was no effect of either pill [$F(1, 75) = 0.01, p = 0.94$] or trial type [$F(1, 75) = 0.51, p = 0.48$]
228 on LOC similarity, suggesting that the trial type differences in CA23DG were not driven by visual similarity.

229 Although there was no pill effect on pattern similarity, the relationship between CA23DG similarity and
230 subsequent associative memory did differ between pills (Figure 4C). Specifically, we observed a similarity
231 by pill interaction [$F(1, 68) = 5.37, p = 0.024$], as well as a marginal three-way interaction among similarity,
232 pill, and trial type [$F(1, 68) = 3.40, p = 0.070$]. Whereas CA23DG similarity *negatively* predicted memory un-
233 der placebo (consistent with more distinct neural representations supporting more precise memories), it
234 *positively* predicted memory under hydrocortisone [$\beta = 32.2[12.7], t(68) = 2.53, p = 0.014$]. This pattern was
235 not present for CA1, as there was no main effect of pattern similarity on memory, nor interactions with trial
236 type or pill ($p_s > 0.20$).

237 Given that associative memory related to subjective affect, we next examined whether CA23DG similar-
238 ity predicted arousal or the change in affect ratings. There were no reliable associations between similarity
239 and arousal ($p_s > 0.10$). However, CA23DG similarity did relate to the cortisol-induced shift towards pos-
240 itive valence. Increased CA23DG similarity with hydrocortisone tracked increased happiness ratings with
241 hydrocortisone for emotional, but not neutral, associations [$F(1, 22) = 5.14, p = 0.034$; Figure 4D].

242 Together, these data suggest that hydrocortisone reverses the relationship between neural similarity
243 and memory. Consistent with prior work (e.g., *LaRocque et al., 2013*), CA23DG similarity negatively predicted
244 memory under placebo; this may reflect the computational need for episodic memory to separate memo-
245 ries encoded in a similar temporal context, in order to reduce interference across those memories at test.
246 Intriguingly, however, we observed a positive relationship between similarity and memory under cortisol,
247 suggesting that cortisol may lead memories to be encoded in a fundamentally different, integrated fashion.
248 Relatively greater pattern similarity was also associated with increased “happy” ratings under cortisol, but
249 this effect was specific to emotional associations. Together, these results suggest a distinct hippocampal
250 mechanism for promoting emotionally salient memories under cortisol.

251 **Hydrocortisone blunts hippocampal subsequent memory effects**

252 Our primary interest in the current study was understanding how intra-hippocampal functional connectivity
253 and representations change with hydrocortisone and contribute to later memory. However, prior work has
254 focused on univariate effects of stress and cortisol, including demonstrating that stress alters hippocampal
255 subsequent memory effects (i.e., greater hippocampal univariate activity for later remembered versus for-
256 gotten items; *Henckens et al., 2009; Qin et al., 2012*). To facilitate comparison with prior work, we thus ran
257 general linear models contrasting subsequently remembered versus forgotten trials (separately for each
258 participant, pill, and trial type; Supplemental Figure S4).

259 In the whole hippocampus, there was no main effect of pill or trial type, nor an interaction between the
260 two ($p_s > 0.30$). However, we observed a numerically positive subsequent memory effects for both trial types
261 under placebo. Collapsing across trial types revealed a reliable subsequent memory effect under placebo
262 [Mean difference = 1.36; SD = 3.24; $t(24) = 2.10, p = 0.046$], consistent with prior work (e.g., *Davachi et al.,*
263 **2003**). In contrast, although there was not a significant difference between hydrocortisone and placebo
264 [$t(24) = -0.69, p = 0.50$], there was no reliable subsequent memory effect for memories encoded under cor-
265 tisol [Mean difference = 0.38; SD = 4.75, $t(25) = 0.41, p = 0.68$]. Considering these effects within hippocampal
266 subfields, we found a similar pattern in CA23DG, but not CA1, consistent prior work and the the proposed
267 role of CA23DG in supporting distinct episodic memories (*Eldridge et al., 2005; Carr et al., 2010*). Together,

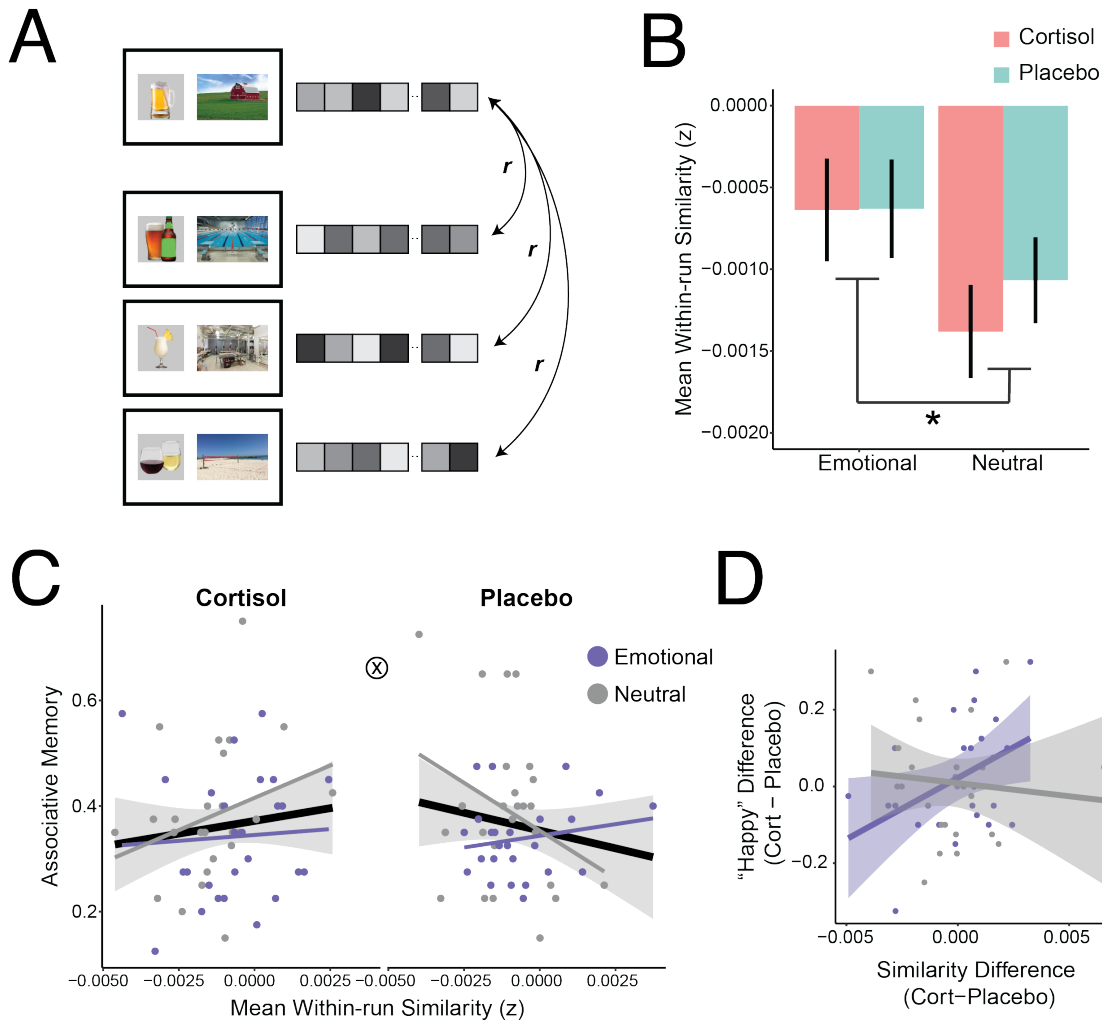


Figure 4. Within-run Pattern Similarity Results. A) We extracted the spatiotemporal pattern associated with each encoding trial. We then correlated each trial to all other trials (averaging the correlations across trials) to obtain a global pattern similarity metric. B) CA23DG pattern similarity differed by trial type, with relatively greater neural similarity among emotional associations. C) CA23DG pattern similarity predicted subsequent associative memory in opposing directions under cortisol versus placebo. D) The difference in CA23DG similarity from cortisol to placebo positively predicted the cortisol-induced increase in happiness ratings from emotional, but not neutral associations. B: Error bars indicate standard error of the mean across participants; * $p < 0.05$. C-D: Error shading indicates 95% confidence interval around the best fit line. Individual colored lines indicate the line of best fit within each trial type.

268 these results converge with prior demonstrations that stress can alter hippocampal memory formation
 269 (*Henckens et al., 2009; Qin et al., 2012*).

270 Discussion

271 In the current study, we combined behavior, high-resolution imaging of the human hippocampus, and phar-
 272 macological manipulation of hydrocortisone to provide novel insight into how hippocampal circuitry and
 273 representations scaffold memory enhancements under stress. First, we demonstrated behaviorally that
 274 cortisol enhances encoding of subjectively emotionally arousing memories. We then demonstrated a role
 275 for cortisol in enhancing functional interactions between hippocampal subfields; this intra-hippocampal
 276 connectivity supported memory under placebo and selectively supported emotional memory under cortisol.
 277 Lastly, we demonstrated that cortisol can alter the way that memories are encoded into the hippocampus,
 278 shifting the relationship between neural similarity and memory from negative under placebo to positive un-

279 der cortisol. Together, these data provide evidence that mechanisms *within* the hippocampus can support
280 memory enhancements under stress.

281 Our behavioral findings build on prior demonstrations that subjective affect and cortisol interact to pro-
282 mote memory encoding. Although cortisol administration prior to encoding did not impact memory per-
283 formance overall, cortisol enhanced memory for participants who experienced greater subjective arousal.
284 This arousal-specific enhancement of memories under stress has been demonstrated previously and high-
285 lights the importance of assessing subjective responses to stimuli when measuring stress effects on mem-
286 ory (**Buchanan and Lovallo, 2001; Abercrombie et al., 2003, 2006; Goldfarb et al., 2019**). However, many
287 of these prior studies focused on negative affect (**Abercrombie et al., 2003, 2006; Goldfarb et al., 2019**).
288 By using emotionally salient stimuli (alcoholic beverages) that could be perceived as either positive or nega-
289 tive, we demonstrated that cortisol is particularly beneficial for remembering emotionally arousing, positive
290 episodes. This finding adds to burgeoning literature that acute stress strengthens the formation of positive
291 emotional memories (**Kamp et al., 2019**), and accords with prior work outside the stress domain demonstrat-
292 ing that positive emotion can bolster associative memory (**Madan et al., 2019**). Relatedly, cortisol amplified
293 the perceived emotional salience of encoded memoranda, with participants becoming less likely to rate en-
294 coded associations as “neutral” (similar to **Abercrombie et al., 2003**). Importantly, this cortisol-induced shift
295 in affect valuation was specific to the encoded associations, and did not reflect a broader hydrocortisone-
296 induced change in affect (as shown with PANAS scores). Together, these results are consistent with past
297 studies showing stress and cortisol-induced enhancements in encoding emotionally arousing experiences
298 and provide a key extension by demonstrating the modulatory role of positive affect.

299 By combining these behavioral metrics with neuroimaging data, we provided insight into hippocampal
300 mechanisms underlying these cortisol-associated memory enhancements. Our use of high-resolution fMRI
301 enabled us to probe the representations of hippocampal subfields, inspired by rodent findings of diver-
302 gent stress effects across subfields (e.g., **Alkadhi, 2019**) and human structural imaging results delineating
303 subfield-specific effects of chronic stress and posttraumatic stress disorder (**Wang et al., 2010; Nolan et al.,**
304 **2020; Weis et al., 2021**). This approach enabled precise localization of hippocampal contributions (rather
305 than aggregating across the whole hippocampus; e.g. **van Stegeren, 2009; Lovallo et al., 2010; Qin et al.,**
306 **2012**). Furthermore, using a within-participant pharmacological manipulation, we interrogated the specific
307 role of cortisol in altering encoded memory representations. In doing so, we reveal novel avenues for hydro-
308 cortisone to enhance hippocampal function to promote later memory, thus pushing against arguments that
309 stress impairs hippocampal function and shifts memory toward other neural substrates (**Kim and Diamond,**
310 **2002; Schwabe et al., 2022**).

311 We identified a novel role for glucocorticoids in enhancing human hippocampal function: Cortisol was
312 associated with increased communication both among hippocampal subfields. This finding builds on prior
313 rodent work suggesting that stress may alter (**Jacinto et al., 2013**) or enhance (**Stepan et al., 2012**) memory-
314 related theta oscillations within the hippocampus. Importantly, our observed enhancement was specific to
315 the hippocampal circuit; connectivity between the hippocampus and amygdala was not altered by exoge-
316 nous hydrocortisone. Although this may be surprising given prior work demonstrating that stress enhances
317 hippocampal-amygdala connectivity (**Ghosh et al., 2013; Vaisvaser et al., 2013**), the full stress response in-
318 cludes many processes in addition to cortisol (for example, adrenergic effects on the amygdala play an im-
319 portant role in modulating cortisol effects on the hippocampus; see **Joëls and Baram, 2009**). Cortisol alone
320 can even reduce hippocampal-amygdala coupling (**Henckens et al., 2012**). This also highlights a limitation
321 in generalizing our focus on cortisol to effects of the multifaceted stress response.

322 In addition to a broad enhancement with hydrocortisone, we found that intra-hippocampal connec-
323 tivity related to memory performance under both cortisol and placebo conditions. Under placebo, intra-
324 hippocampal (CA1-CA23DG) connectivity positively predicted memory for neutral associations, consistent
325 with the theorized role for this circuit in supporting episodic memories (**Schapiro et al., 2017**). Under cor-
326 tisol, in contrast, connectivity positively predicted memory for emotional associations, but negatively for
327 neutral associations. This finding may suggest that the “typical” intrahippocampal mechanism supporting
328 successful memory encoding is repurposed under cortisol to prioritize memory for emotional associations.
329 Highlighting the importance of the emotional nature of these associations, connectivity under cortisol also

330 tracked subjective arousal and valence. Interestingly, the directionality of connectivity/behavior associa-
331 tions differed between emotional and neutral trial types, despite behavioral evidence that arousal broadly
332 tracks memory across trial types. Future work is needed to understand stress and emotion-induced changes
333 in hippocampal encoding mechanisms, and what neural mechanism supports cortisol-induced enhance-
334 ments in memory for putatively neutral stimuli.

335 The connectivity results indicate a common mechanism supporting memory: intra-hippocampal connec-
336 tivity broadly promotes memory under placebo, but selectively promotes emotional memory under corti-
337 sol. In contrast, the pattern similarity findings indicate diverging hippocampal encoding processes. Under
338 placebo, pattern *dissimilarity* predicted better subsequent memory. This finding is consistent with prior
339 empirical work (**LaRocque et al., 2013; Favila et al., 2016; Chanales et al., 2017; Wanjia et al., 2021**) and
340 theoretical models of hippocampal function, which posit that distinct neural representations are needed
341 to support episodic memory (**McClelland et al., 1995; Brunec et al., 2020**). In contrast, under cortisol, rela-
342 tively greater pattern *similarity* predicted memory. This pattern is similar to one recently observed in the
343 amygdala (**Bierbrauer et al., 2021**). Closer examination of our data suggest an affect-driven mechanism.
344 First, although the similarity-memory association did not interact with trial type, greater similarity broadly
345 tracked enhanced emotional memory (irrespective of pill). Second, we observed overall greater similarity
346 for emotional compared to neutral stimuli (again, irrespective of pill). This did not appear to be driven by
347 perceptual or semantic features, as this pattern was not observed in lateral occipital cortex. These results
348 may converge with prior demonstrations that greater pattern similarity at encoding (across a range of brain
349 regions, including the hippocampus) predicts better emotional memory (**Visser et al., 2013; Tambini et al.,**
350 **2017**). Thus, one interpretation of the similarity/memory relationships for neutral memoranda (i.e., neg-
351 ative under placebo but positive under hydrocortisone) is that, with hydrocortisone, emotional encoding
352 mechanisms are engaged to support neutral memory as well. Together, these data suggest that memory
353 formation under cortisol may be supported by distinct underlying computations. Whereas distinctive mem-
354 ory representations may support memory encoding under typical circumstances, more similar memory
355 representations may benefit memory with cortisol.

356 Considered together, the connectivity and pattern similarity analyses provide evidence that the hip-
357 pocampus can indeed support enhanced memory formation under hydrocortisone. Importantly, these two
358 signals may serve distinct encoding purposes: intra-hippocampal connectivity primarily explained memory
359 for emotionally salient associations, and CA23DG similarity primarily accounted for memory for neutral
360 information. Importantly, despite robust evidence that the hippocampus can support memory encoding
361 under hydrocortisone, we found evidence for a blunted univariate subsequent memory effect in the hip-
362 pocampus. Although we interpret these results with caution, given that the difference between placebo
363 and hydrocortisone was not significant, this is consistent with past reports (**Qin et al., 2012**). Although dis-
364 rupted subsequent memory effects have been interpreted as evidence against hippocampal involvement in
365 stress-induced memory enhancements, our findings challenge this interpretation. Despite replicating this
366 canonical “negative hippocampal” result, we also provide evidence that intrahippocampal function under
367 cortisol can indeed predict subsequent memory. By uncovering positive cortisol effects on hippocampal
368 function, our results highlight the importance of considering multiple hippocampal encoding mechanisms
369 when assessing the effects of cortisol and stress on memory. Whereas cortisol may impair some hippocam-
370 pal encoding mechanisms, it may yet enhance or alter other avenues by which the hippocampus drives
371 successful memory.

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377 **Author contributions**

378 E.V.G. and R.S. conceived the study. E.V.G. and B.B.H. designed the experiments. B.B.H. performed the exper-
379 iments. E.V.G. and R.S. supervised data collection. N.B.T-B. contributed imaging sequences and analysis
380 pipelines. E.V.G., B.E.S., and N.B.T-B. conceived behavioral and neural analyses. B.B.H. organized and pro-
381 cessed the behavioral data. E.V.G. and B.B.H. preprocessed the fMRI data. B.E.S. carried out subsequent
382 analyses on the behavioral and fMRI data. B.E.S. and E.V.G. wrote the manuscript with assistance from
383 B.B.H. All authors edited the manuscript.

384 **Declaration of Interests**

385 The authors declare no competing interests.

386 **Methods**

387 **Participants**

388 Twenty-seven healthy, right-handed human participants (16 male; mean age 27.6; range 21-44) completed
389 all five sessions of the experiment. This sample size was determined by a power analysis from pilot data
390 indicating that associations between cortisol and memory could be observed with $N = 25$ (G^* Power: cor-
391 relation = .508, power = 0.85). One participant's Week 2 data were excluded from all analyses because of
392 technical error (they were shown different stimuli at encoding and retrieval).

393 Participants were recruited from the New Haven community via online advertisements and flyers. All
394 participants were fluent in English, had BMI between 18-35 (to ensure standardized metabolism of hydro-
395 cortisone, which is lipophilic), had normal or corrected-to-normal vision, and did not meet criteria for any
396 substance use disorder (excluding caffeine). To reduce factors that could influence their reaction to hydro-
397 cortisone, participants were excluded if they were currently using medications/drugs that interfere with the
398 HPA axis response such as SSRIs, beta-blockers, or corticosteroids. Further, peri- and post-menopausal fe-
399 males, pregnant or lactating females, and those with hysterectomies were excluded. Participants were also
400 excluded based on contraindications for MRI or hydrocortisone tablets. Participants were also required to
401 have had a physical examination within the last 6 months to determine that they could safely complete
402 study procedures; if not, one was administered by a Yale School of Medicine MD. All participants provided
403 written informed consent to complete the study and all procedures were approved by the Yale Institutional
404 Review Board.

405 **Method Details**

406 *Procedure Overview*

407 We employed a double-blind, placebo-controlled, crossover design (Figure 1). At the start of each session,
408 participants provided urine samples to undergo drug and pregnancy testing as well as a breathalyzer to
409 ensure sobriety. All experimental sessions occurred between 12:00pm and 6:00pm to control for circadian
410 fluctuations in cortisol (*Lupien et al., 2007*).

411 After an intake appointment to determine eligibility, participants completed two rounds of encoding
412 (Day 1) and memory retrieval (Day 2, 24h later). These rounds were separated by an average of 16.22 days
413 ($SD = 14.53$). Prior the encoding session, participants received a tablet containing either 20mg hydrocorti-
414 sone or a visually identical placebo pill compounded by the Yale Investigational Drug Service (order coun-
415 terbalanced; see Hydrocortisone Administration and Cortisol Measurement: Randomization). Functional
416 magnetic resonance imaging (fMRI) data were acquired during each encoding session along with salivary
417 samples to measure peripheral cortisol. Participants were instructed not to consume alcohol for 24h prior
418 to fMRI sessions.

419 *Intake Appointment*

420 After providing informed consent, participants underwent the Structured Clinical Interview for the DSM-5
421 or SCID (*First, 2014*) with a trained interviewer to determine if they had ever met criteria for a substance use

422 disorder (SUD) or alcohol use disorder (AUD; N = 3 excluded following intake due to past or present endorse-
423 ment of AUD). Sobriety was confirmed via breathalyzer at each visit. To further classify drinking behavior,
424 participants completed the AUDIT (**Bush et al., 1998**) administered by an experimenter and answered the
425 Alcohol Severity Index Questionnaire, ASI (**Mäkelä, 2004**), via self-report on an experiment computer.

426 Participants also self-reported on general demographic information and filled out a series of question-
427 naires including the Positive Affect Negative Affect Scale, PANAS (**Watson et al., 1988**). If deemed fully eligible
428 at intake, participants were scheduled for the four sessions of the experiment.

429 *Tasks*

430 **Encoding.** During the fMRI sessions, participants performed an encoding task similar to **Goldfarb et al.**
431 (**2020**). On each trial, participants viewed object and scene photographs and were asked to vividly imagine
432 the object as part of the scene (5s). They then indicated how they felt when imagining each object/scene
433 pair using an MR-compatible button box, reporting their valence (unhappy, happy, or neutral) and arousal
434 (how intensely they felt that way; 1 = not at all; 4 = extremely), and how much they wanted an alcoholic drink
435 (1 = not at all; 4 = a lot; 2s per response). Responses were displayed in green. Trials were separated by a
436 jittered ITI from a geometric distribution (mean = 2s). All task stimuli were presented with MATLAB using
437 the Psychophysics Toolbox (**Brainard, 1997; Pelli, 1997**).

438 Participants completed two blocks of encoding during each scanning session, and each block contained
439 40 object-scene pairs. Critically, the two blocks differed in the type of objects presented. One block con-
440 tained emotionally salient alcohol-related object images (e.g., a glass of wine) and the other block contained
441 neutral, handheld object images (e.g. a tape measure; further details regarding stimuli below). The order of
442 encoding blocks was counterbalanced across participants. Participants were informed that their memory
443 for object-scene pairs would be tested the following day.

444 **Retrieval.** Participants returned 24 hours after each encoding session for a series of memory tests. As
445 stress and cortisol generally impair memory retrieval (**Gagnon and Wagner, 2016**), this timing allowed us to
446 target hydrocortisone effects on memory encoding while avoiding lingering effects on retrieval processes.
447 Memory tests were separated by trial type and occurred in the same order as encoding (i.e., if participants
448 encoded emotional object-scene pairs first, they retrieved emotional memoranda first). No fMRI data were
449 collected at retrieval.

451 **Object Recognition.** To assess memory for individual objects, participants first viewed all objects from en-
452 coding (N = 80) intermixed with novel foils from the same object subcategories (N = 80). After viewing each
453 object (3s), participants indicated whether they thought the image was old (from the encoding session the
454 day before) or new. Responses were on a 4-point scale (“confident old”, “unsure old”, “unsure new”, “confi-
455 dent new”; 2s per response, 0.5s ITI).

457 **Associative Memory.** To assess memory for the object-scene pairings, participants were shown an object
458 image from encoding. They were first asked if it was paired with an indoor or outdoor scene (maximum
459 response time 2s). They were then shown the same object image along with four scenes (2s): the orig-
460 inal scene paired at encoding, a different scene presented at encoding to control for familiarity, and two
461 matched perceptual lures (one lure per encoded scene). Participants indicated with which of the four scenes
462 the object was paired (up to 4s). They were told that if they remembered what scene was shown with the
463 object, but not exactly which image was displayed, to make their best guess between the two images depict-
464 ing that scene. Pairing the scenes with perceptually matched foils allowed us to dissociate more general,
465 or gist-based memories (e.g., the picture I saw was a beach) versus specific associative memories (e.g., the
466 picture I saw was *that* beach). They were last asked how confident they were in their memory for the scene
467 (1 = “not at all”; 4 = “extremely”; up to 2s). Questions were separated by an ISI of .5s. Choosing the correct,
468 specific scene from encoding denoted correct associative memory.

470

471 *Task Stimuli*

472 **Objects.** A total of 400 photographs of emotionally salient alcohol and neutral handheld stimuli were ob-
473 tained from prior studies (*Dunsmoor et al., 2012; Fey et al., 2017; Van Der Linden et al., 2015; Sinha et al.,*
474 **2022**) and from Google image searches. All images were edited to appear on a grey background with visible
475 text occluded and were resized to 200 x 200 pixels. Images were chosen to be perceptually distinct from
476 one another and were evenly distributed into four subcategories (alcohol: beer, wine, liquor, and mixed
477 drinks; neutral: items likely to be found in a kitchen, garage, bathroom, and office). A separate validation
478 experiment was conducted to select a subset of 320 images matched on perceptual (e.g., level of detail
479 (*Dager et al., 2014*) and familiarity (*Bainbridge et al., 2017*)), but not affective features. We chose not to
480 match stimuli on valence or arousal, as we aimed for emotional, but not neutral, stimuli to induce affect.

481

482 **Scenes.** A total of 320 indoor and outdoor scene images were obtained from the SUN database (*Xiao et al.,*
483 **2010**) and Google Image searches. Specifically, we obtained 80 indoor and 80 outdoor scene images, each
484 with a perceptual match (e.g., 2 pictures of beaches) that served as a foil during the associative memory
485 test. As with object stimuli, a separate validation sample was collected to confirm that perceptual similarity
486 across pairmate images was matched.

487 *Hydrocortisone Administration and Cortisol Measurement*

488 **Randomization.** After intake, participants were pseudorandomly assigned to receive either hydrocortisone
489 or placebo prior to their first encoding session, taking into account their age, sex, level of education, and
490 drinking level. Pill order was determined by an unblinded statistician, leaving the experimenter (B.B.H.)
491 blind to participant condition.

492

493 **Pill Administration.** Across the two weeks, participants received one oral tablet of hydrocortisone 20mg
494 and one oral tablet of placebo (sucrose). The two pills were physically identical. The order of pill admin-
495 istration (week 1 or 2) was counterbalanced by an unblinded statistician, with all additional experimental
496 personnel and participants blinded for the duration of the study. Pills were compounded by the Yale Inves-
497 tigational Drug Service and stored at 20-25C. Pills were administered approximately one hour prior to the
498 start of the first encoding run (consistent with *Buchanan and Lovallo, 2001*).

499

500 **Measuring cortisol levels.** Participants provided six salivary samples over the two fMRI sessions (3 per
501 session) to measure cortisol concentration. The baseline sample was obtained approximately 10 minutes
502 after arrival (after acclimation to the environment and prior to pill administration). The encoding sample
503 was obtained immediately prior to the first encoding run, approximately 1 hour after pill administration.
504 The final sample was obtained after participants exited the scanner. Samples were collected using Starst-
505 edt Salivate Tubes and samples were processed by the Yale Center for Clinical Investigation (YCCI) using
506 radioimmunoassay (RIA).

507

508 **Measuring Awareness.** To measure subjective awareness of pill administration, participants reported
509 which pill they thought they had received (response options: Cortisol, Placebo, or Not Sure). This was only
510 asked on pill administration (scan) days, both immediately after consuming the pill and after the fMRI scan.

511 *fMRI Procedure*

512 Participants underwent fMRI scanning after pill administration on both days. Specifically, participants per-
513 formed the encoding task (described above) while BOLD fMRI data were acquired. We additionally collected
514 a localizer run and resting-state fMRI scans.

515

516 **Localizer Run.** Prior to encoding, participants completed a 6-min run in which they viewed images (1s
517 each, 0.5s ITI) and were instructed to button press anytime an image repeated twice in a row (1-back). They
518 viewed 8 blocks of 22 images each. The blocks consisted of scenes, emotionally salient alcoholic beverages,
519 neutral handheld objects, or phase-scrambled versions of the alcohol and neutral images. None of these

520 images were repeated in the subsequent encoding task. Each category appeared twice during the 8 blocks
521 in a randomized order per subject.

522

523 **Rest Runs.** Participants underwent three 6-minute rest scans throughout each session: one prior to encod-
524 ing (after the localizer run) and one immediately after each encoding run. No data from these rest runs are
525 reported in the current paper.

526 *MRI Acquisition Parameters*

527 Data were acquired on Siemens 3T Prisma scanners using a 64-channel coil at the Magnetic Resonance
528 Research Center at Yale University. Data were acquired across three scanners (N = 6 on scanner A, N = 2 on
529 scanner B, N = 19 on scanner C). Each participant completed both of their MRI sessions on a single scanner.
530 Parameters were the same across scanners. Functional images were acquired using an echoplanar imaging
531 (EPI) sequence with the following parameters: TR = 1000ms, TE = 30ms, 75 axial slices, voxel size = 2x2x2
532 mm, flip angle = 55 degrees, multiband factor = 5, interleaved acquisition, FOV: 220x220.

533 Anatomical data were acquired using one T1-weighted 3D MPRAGE sequence (TR = 2400ms, TE = 1.22ms,
534 208 sagittal slices, voxel size = 1x1x1 mm, flip angle = 8 degrees, FOV: 256x256) and one T2-weighted turbo
535 spin echo (TR=11170 ms, TE = 93ms, 54 coronal slices, voxel size = 0.44 x 0.44 x 1.5mm, distance factor=20%,
536 flip angle = 150 degrees).

537 **Quantification and Statistical Analysis**

538 *fMRI Preprocessing*

539 fMRI data were preprocessed using FSL 6.0.1. All encoding runs met criteria for inclusion based on motion
540 (defined a priori as >1.5mm absolute mean frame-to-frame displacement, as computed by FSL's MCLFIRT;
541 **Jenkinson et al., 2002**). Data were skull-stripped (BET; **Smith, 2002**), pre-whitened (FILM; **Woolrich et al.,**
542 **2001**), and high-pass filtered at 0.01 Hz to remove low-frequency signal drift. We then used FSL's FEAT () to
543 run a GLM per run to control for motion and covariates of no interest. Regressors included 6 linear esti-
544 mated motion parameters and white matter timeseries (each plus temporal derivatives) and stick function
545 regressors for nonlinear motion outliers. No smoothing was applied.

546 For background connectivity analyses (see below), we additionally removed trial-evoked signal (image
547 on/offset and button presses modeled using boxcars convolved with a double-gamma HRF, plus temporal
548 derivatives).

549 In all analyses, model residuals were aligned to a reference functional scan and then to the participant's
550 high-resolution T1 anatomical scan using boundary based registration (**Greve and Fischl, 2009**). The high-
551 resolution T2 anatomical image (used for defining hippocampal subregions; see below) was also registered
552 to the participant's T1 anatomical scan using FSL's FLIRT (**Jenkinson and Smith, 2001**).

553 *Regions of Interest Definition*

554 Hippocampal subfields and medial temporal lobe cortical regions were defined individually for each par-
555 ticipant primarily based on their T2-weighted anatomical images. Segmentation was done automatically
556 (using both the T1- and T2-weighted anatomical images) using the automated segmentation of hippocam-
557 pus subfields (ASHS) software package (**Yushkevich et al., 2015**). We used an atlas containing 51 manual
558 segmentations of hippocampal subfields (**Aly and Turk-Browne, 2016a,b**). The automated segmentations
559 were visually inspected for quality assurance and in 4 cases when automatic segmentation was particularly
560 poor, manual segmentation was performed. Manual segmentation was performed using the procedure
561 (i.e., using the same anatomical landmarks) as the segmentations which comprised the atlas (**Insausti et al.,**
562 **1998; Pruessner et al., 2002; Duvernoy, 2005**), as described in detail in **Aly and Turk-Browne (2016b)**. The hip-
563 pocampus was segmented into CA1, CA2/3, and dentate gyrus (DG) subfields; medial temporal lobe cortex
564 was segmented into entorhinal cortex (EC), perirhinal cortex (PRC), and parahippocampal cortex (PHC). For
565 analysis purposes, the CA2/3 and DG subfields were concatenated into a single CA23DG subfield. Further,
566 a whole hippocampus ROI was constructed by concatenating the CA23DG, CA1, and subiculum ROIs. One

567 participant did not have a high-resolution T2-weighted image, and thus their hippocampal subfields could
568 not be segmented; this participant was excluded from all neural analysis looking at the hippocampus.

569 In addition to MTL ROIs, we analyzed data from amygdala and lateral occipital cortex (LOC). Anatomical
570 amygdala ROIs were defined for each participant based on their T1 MPRAGE scans using FSL's FIRST
571 automated segmentation tool (**Patenaude et al., 2011**). LOC ROIs were functionally defined based on the localizer scan. These data were preprocessed as described above for encoding runs, then residuals were smoothed
572 (6mm FWHM), and entered into subject-level GLMs to extract beta values per block type (emotionally salient
573 objects, neutral objects, scenes, and phase-scrambled images). These subject-level estimates were aligned
574 to MNI space and entered into a group-level ANOVA (AFNI's 3dANOVA3) as a function of pill and image
575 type. LOC was defined from a post-hoc contrast of neutral objects vs. scrambled images, cluster-corrected
576 ($p < .001$, $\alpha = .05$, AFNI's 3dClustSim) and then masked with the Harvard-Oxford Probabilistic Atlas definition
577 for LOC (50% threshold). This mask was then aligned to each participant's functional data.
578

579 *Background Connectivity Analysis*

580 To examine fluctuations among hippocampal subfields during encoding, we conducted a background connectivity analysis (e.g., **Norman-Haignere et al., 2012; Al-Aidroos et al., 2012; Córdova et al., 2016**). After
581 regressing out the task-evoked signal from each fMRI run as described above, we extracted the mean residual timeseries across voxels in each ROI. We then correlated the timeseries between pairs of ROIs. These
582 correlations were then normalized using a Fisher r -to- z transform for further analysis.
583
584

585 *Representational Similarity Analysis*

586 To probe the representational content of encoded associations in the hippocampus, we computed within-run global pattern similarity (similar to **LaRocque et al., 2013; Tompary and Davachi, 2017; Cowan et al., 2020**). For each encoded association, we extracted the associated pattern of activity per ROI across voxels
587 and time (5 TRs during which the object-scene pair was on screen). To account for the hemodynamic lag, we shifted the data by 5s (5 TRs), such that the extracted pattern reflected the BOLD activity 5-10s after
588 the true onset. We then correlated these spatiotemporal vectors among all pairs of trials within a run and computed the average correlation. As in the background connectivity analyses, we then normalized these
589 averaged correlations via Fisher r -to- z transform.
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594 *Univariate Subsequent Memory Analysis*

595 To examine whether hippocampal activation differentiated subsequently remembered versus forgotten associations, we conducted a univariate subsequent memory analysis (e.g., **Davachi et al., 2003**). We first
596 smoothed the residuals from the preprocessing models above (6mm FWHM) and then ran a separate GLM
597 for each encoding run for each participant. We included separate regressors for subsequently remembered versus forgotten trials plus their temporal derivative. Each trial was modeled as a boxcar (with a duration
598 of 5s), convolved with a double-gamma HRF. We then computed the contrast between subsequently remembered versus forgotten associations. For each ROI, we extracted these contrast estimates
599 averaged across voxels within the ROI, separately for each trial type and pill. We refer to this difference as the "Subsequent Memory Effect".
600
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603

604 *Statistical Modeling*

605 All statistical analyses were conducted as linear mixed effect models and were performed in R (version
606 4.1.3) using the `nlme` package (**Pinheiro et al., 2022**). All models treated participant as a random effect, such that a random intercept was computed for each participant. For analyses that examined the effects of trial
607 type and pill, we additionally included covariates of week, pill order, and trial type order. For analyses that examined a difference between cortisol and placebo, we included covariates of pill order and trial type
608 order. Follow-up tests were performed using the `emmeans` package (**Lenth, 2022**), with the exception of the subsequent memory effect analyses, in which we used one-sample t -tests to quantify whether remembered
609 versus forgotten contrasts differed from 0.
610
611
612

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