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Behavioral/Cognitive

Hippocampal Mechanisms Support Cortisol-Induced Memory Enhancements

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Stress can powerfully influence episodic memory, often enhancing memory encoding for emotionally salient information. These stress-induced memory enhancements stand at odds with demonstrations that stress and the stress-related hormone cortisol can negatively affect the hippocampus, a brain region important for episodic memory encoding. To resolve this apparent conflict and determine whether and how the hippocampus supports memory encoding under cortisol, we combined behavioral assays of associative memory, high-resolution fMRI, and pharmacological manipulation of cortisol in a within-participant, double-blinded procedure (in both sexes). Behaviorally, hydrocortisone promoted the encoding of subjectively arousing, positive associative memories. Neurally, hydrocortisone led to enhanced functional connectivity between hippocampal subregions, which predicted subsequent memory enhancements for emotional associations. Cortisol also modified the relationship between hippocampal representations and associative memory: whereas hippocampal signatures of distinctiveness predicted memory under placebo, relative integration predicted memory under cortisol. Together, these data provide novel evidence that the human hippocampus contains the necessary machinery to support emotional associative memory enhancements under cortisol.

Key words: **associative memory; cortisol; emotional memory; fMRI; functional connectivity; stress**

Significance Statement

Our daily lives are filled with stressful events, which powerfully shape the way we form episodic memories. For example, stress and stress-related hormones can enhance our memory for emotional events. However, the mechanisms underlying these memory benefits are unclear. In the current study, we combined functional neuroimaging, behavioral tests of memory, and double-blind, placebo-controlled hydrocortisone administration to uncover the effects of the stress-related hormone cortisol on the function of the human hippocampus, a brain region important for episodic memory. We identified novel ways in which cortisol can enhance hippocampal function to promote emotional memories, highlighting the adaptive role of cortisol in shaping memory formation.

Introduction

Stress transforms the way we encode and consolidate experiences into memory, often impairing memory for neutral, non–stress-relevant information, yet enhancing memory for emotionally salient or stress-relevant experiences (Joëls et al., 2006; McGaugh, 2015; Shields et al., 2017; Goldfarb, 2019). Such stress-related emotional memory enhancements have been linked to stress-induced glucocorticoid release (cortisol in humans; corticosterone in rodents) in both rodents (Okuda et al., 2004; Roozendaal et al., 2006; Shors, 2006; Sandi and Pinelo-Nava, 2007) and humans (Buchanan and Lovallo, 2001; Abercrombie et al., 2006; Kuhlmann and Wolf, 2006; Schwabe et al., 2008; S. Segal et al., 2014). However, pinpointing the neural mechanisms underlying this selective strengthening of emotional memory with glucocorticoids presents a puzzle.

One possibility is that memory enhancements under stress are supported by a fundamentally different mechanism than memory encoding without stress. Although the hippocampus critically supports episodic memory under nonstress conditions (Davachi, 2006), glucocorticoids and stress can broadly reconfigure

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which neural systems support memory (M. Segal et al., 2010; Goldfarb and Phelps, 2017; Schwabe et al., 2022). Thus, many stress-induced emotional memory enhancements, particularly those involving the noradrenergic component of the stress response (Bahtiyar et al., 2020), are attributed to amygdala-based mechanisms (Roozendaal et al., 2009; Bierbrauer et al., 2021), including enhanced hippocampal–amygdala interactions (Roozendaal and McGaugh, 1997; Kim et al., 2001; Ghosh et al., 2013; Vaisvaser et al., 2013; de Voogd et al., 2017).

Another possibility is that glucocorticoids directly act on the hippocampus to enhance memory. Indeed, the hippocampus is highly sensitive to glucocorticoids, in part because of high receptor density (Seckl et al., 1991; Lupien et al., 2007; Wang et al., 2013). However, glucocorticoid effects on the hippocampus are not straightforward. For example, glucocorticoids have been linked to both impairments and enhancements of hippocampal LTP (Kim and Diamond, 2002; Joëls et al., 2006). In humans, the glucocorticoid hormone cortisol has similarly mixed effects on hippocampal BOLD activity (Harrewijn et al., 2020), both decreasing (Pruessner et al., 2008; Lovallo et al., 2010; Bini et al., 2022) and increasing (Symonds et al., 2012; Sinha et al., 2016) hippocampal BOLD. Similarly, acute stress (which increases cortisol levels) can attenuate (Qin et al., 2012) or reverse (Henckens et al., 2009) hippocampal encoding signatures, but has also been linked to increased memory-related oscillations in the medial temporal lobe that potentiate memory (Heinbockel et al., 2021). Behaviorally, stress and cortisol can also enhance associative memory (van Ast et al., 2013, 2014; Goldfarb et al., 2019; Grob et al., 2023), a representation that relies on the rapid binding abilities of the hippocampus (Davachi, 2006). However, whether direct cortisol-induced modulation of hippocampal function can drive these benefits remains unclear.

Here we combine fMRI, behavior, and double-blind hydrocortisone administration to probe whether hippocampal mechanisms support associative memory encoding under cortisol. To achieve this, we focus behaviorally on memory representations that rely on the hippocampus, and leverage imaging and analysis techniques to embrace the functional heterogeneity of the hippocampus. Specifically, we examine associative — rather than item (Wolf, 2009; Shields et al., 2017) — memory, as this requires hippocampal binding between components of each event (Davachi, 2006; Henke, 2010). By using high-resolution fMRI, we can make a critical advance of examining cortisol effects across subfields, as nonhuman animal findings demonstrate distinct stress effects across subfields (Sharvit et al., 2015; Alkadhi, 2019) and human research indicates that subfields support distinct aspects of memory (Duncan and Schlichting, 2018; Sherman et al., 2023). Further, leveraging novel analyses that query the functional connectivity among hippocampal subfields provides circuit-level mechanistic insight (Schapiro et al., 2017) and extends prior work examining hippocampal–amygdala connectivity (Vaisvaser et al., 2013). Last, by examining neural pattern similarity between memoranda, we can assess how cortisol transforms memory representations, enabling us to move beyond claims about how stress broadly activates or deactivates a brain region. Together, these approaches provide a nuanced understanding of how cortisol modulates hippocampal mechanisms supporting associative memory encoding.

Materials and Methods

Participants

Twenty-seven healthy, right-handed human participants (16 male; mean age 27.6; range 21-44 years) completed all five sessions of the experiment. This sample size was determined by a power analysis of pilot data showing associations between cortisol and enhanced memory (G*Power required $N = 25$: correlation = 0.508, power = 0.85). One participant's week 2 data were excluded from all analyses because of a technical error (they were shown different stimuli at encoding and retrieval).

Participants were recruited from the New Haven community via online advertisements and flyers. All participants were fluent in English, had BMI between 18 and 30 (to standardize metabolism of lipophilic hydrocortisone; mean = 23), had normal or corrected-to-normal vision, and did not meet criteria for any substance use disorder (excluding caffeine). To reduce factors that could influence reactions to hydrocortisone, participants were excluded if they were currently using medications/drugs that interfere with the hypothalamic-pituitary-adrenal axis response, such as selective serotonin reuptake inhibitors, β-blockers, or corticosteroids, or based on contraindications for fMRI or hydrocortisone tablets. Further, perimenopausal and postmenopausal females, pregnant or lactating females, and those with hysterectomies were excluded. Females completed a menstrual cycle questionnaire. Three (27% of the female sample) reported taking oral contraceptives, and a further three (27%) were using intrauterine devices. Control analyses revealed no main effects of sex (nor interactions between sex and experimental factors) on any of the behavioral or neural measures of interest.

Because of the pharmacological intervention, participants were required to have had a physical examination within the last 6 months to determine that they could safely complete study procedures; if not, one was administered by a Yale School of Medicine MD. All participants provided written informed consent to complete the study, and all procedures were approved by the Yale Institutional Review Board.

Procedure overview

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

After an intake appointment to determine eligibility, participants completed two rounds of encoding (day 1) and memory retrieval (day 2, 24 h later). Before encoding, participants received a tablet containing either 20 mg hydrocortisone or a visually identical placebo pill compounded by the Yale Investigational Drug Service (order counterbalanced; see Hydrocortisone administration and cortisol measurement: randomization). fMRI data were acquired during encoding along with salivary samples to measure peripheral cortisol. Participants were instructed not to consume alcohol for 24 h before fMRI sessions.

Intake appointment

After providing informed consent, participants underwent the Structured Clinical Interview for the DSM-5 (First, 2014) with a trained interviewer to determine whether they had ever met criteria for a substance use disorder or alcohol use disorder ($N = 3$ excluded following intake because of past or present alcohol use disorder).

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

Tasks

Encoding. During the fMRI sessions, participants performed an encoding task similar to Goldfarb et al. (2020). On each trial, participants viewed object and scene photographs and were asked to vividly imagine the object as part of the scene (5 s). They then indicated how they felt when imagining each object/scene pair using an MR-compatible button box, reporting their valence (unhappy, happy, or neutral) and arousal (how intensely they felt that way; 1 = not at all; 4 = extremely), and how much they wanted an alcoholic drink (1 = not at all; 4 = a lot; 2 s per response). Responses were highlighted in green. Trials were separated by a jittered intertrial interval from a geometric distribution to maximize distinct event-level BOLD signal (mean = 2 s). All task stimuli were

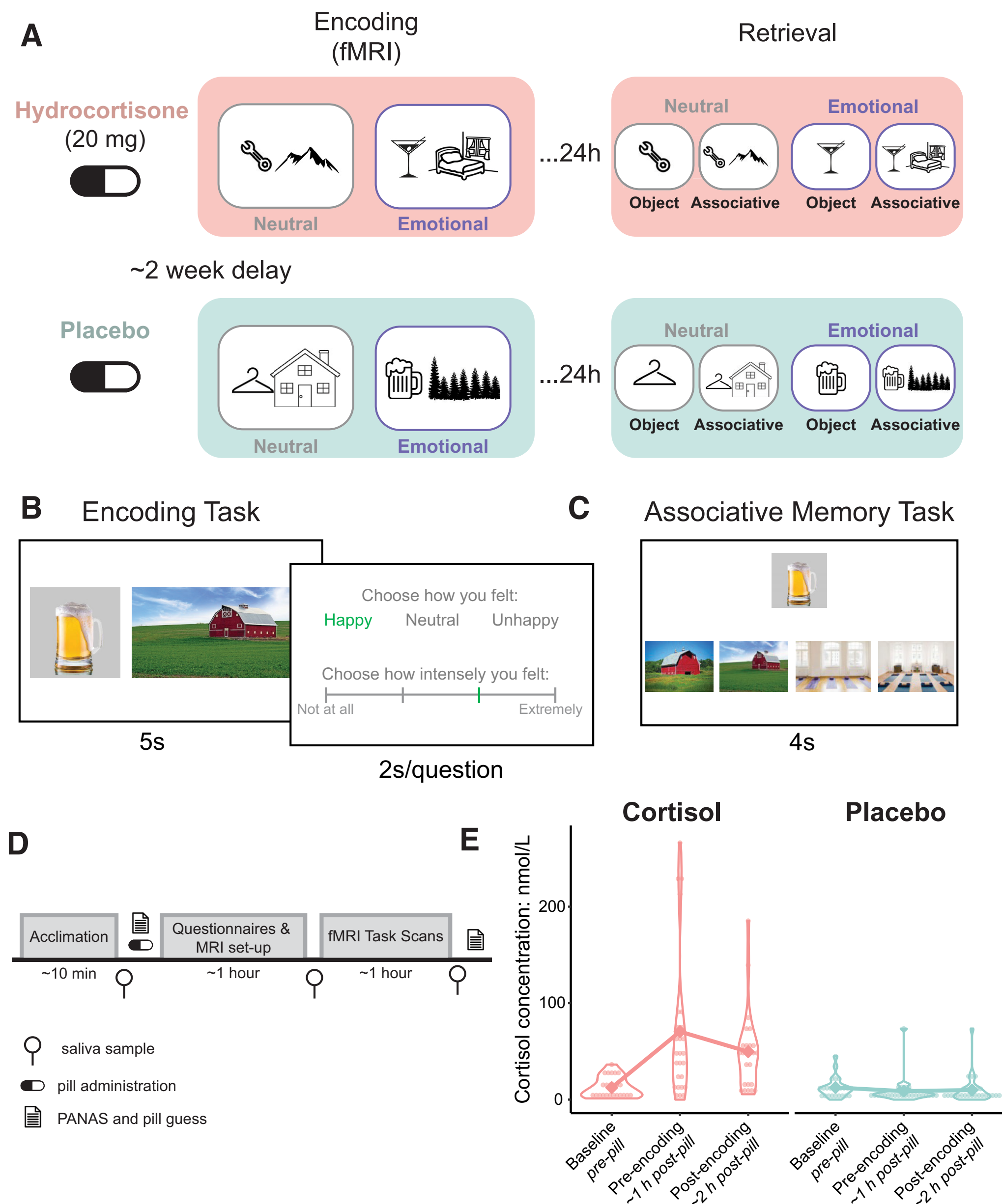

Figure 1. Task design and cortisol assays. ***A***, Participants completed the experimental procedure twice (on two separate weeks; order counterbalanced across participants). They first received a pill containing either 20 mg hydrocortisone or no active substance (placebo). They then completed a memory 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 emotional (alcoholic beverages; order counterbalanced across participants). Each encoding run took ∼9 min. Participants returned 24 h later to be tested on their memory for individual objects (Object Recognition Test; 7.5 min) and object-scene associations (Associative Memory Test; 7 min). ***B***, During encoding, participants viewed an object-scene pair for 5 s, 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. ***D***, Participants provided three saliva samples throughout the encoding session: before pill administration (after a 10 min acclimation period), before encoding (∼1 h post-pill), and after encoding (∼2 h post-pill). They also completed the PANAS and provided a guess as to which pill they received, both before and after the scanning sessions. ***E***, Hydrocortisone led to elevated salivary cortisol concentrations at the two post-pill administration time points, indicating that cortisol was elevated during memory encoding. Small dots represent individual participants. Larger diamonds represent mean across participants.

presented with MATLAB using the Psychophysics Toolbox (Brainard, 1997; Pelli, 1997).

Participants completed two blocks of encoding per scanning session with 40 object-scene pairs. One block (Neutral) contained images of neutral, handheld objects (e.g., a tape measure; further details below), whereas the other block (Emotional) contained alcohol-related objects (e.g., a glass of wine). These alcohol-related images elicit high ratings of arousal and can be interpreted as positive or negative valence (Goldfarb et al., 2020). Emotional and neutral object-scene pairs were presented in separate blocks to promote extended “emotional” versus “neutral” affective states and limit carryover effects (Tambini et al., 2017). Critically, block order (Emotional vs Neutral first) was counterbalanced across participants to avoid systematic order effects. Participants were informed that their memory for object-scene pairs would be tested the following day.

Retrieval. Participants returned 24 h after each encoding session for a series of memory tests. As stress and cortisol generally impair memory retrieval (Gagnon and Wagner, 2016; Antypa et al., 2022), this timing allowed us to target hydrocortisone effects on memory encoding and consolidation while avoiding lingering effects on retrieval processes. Memory tests were separated by block and occurred in the same order as

encoding (i.e., if participants encoded emotional object-scene pairs first, they retrieved emotional memoranda first). For each block, participants first underwent the Object Recognition test, followed by the Associative Memory test. No fMRI data were collected at retrieval.

Object recognition. To assess memory for individual objects, participants first viewed all objects from encoding ($N = 80$) intermixed with novel foils from the same object subcategories ($N = 80$). After viewing each object (3 s), participants indicated whether they thought the image was old (from the encoding session the day before) or new. Responses were on a 4 point scale ("confident old," "unsure old," "unsure new," "confident new"; 2 s per response, 0.5 s intertrial interval).

Associative memory. To assess memory for the object-scene pairings, participants were shown an object image from encoding. They were first asked whether it was paired with an indoor or outdoor scene (maximum response time 2 s). They were then shown the same object image along with four scenes (2 s): the original scene paired at encoding, a different scene presented at encoding to control for familiarity, and two matched perceptual lures (one lure per encoded scene). Participants indicated which of the four scenes was paired with the object (up to 4 s) and rated their confidence in their memory (on a 4 point scale, from "Not at all" to "Very"; up to 2 s). They were told that, if they remembered what scene was shown with the object, but not exactly which image was displayed, to make their best guess between the two images depicting that scene. Pairing the scenes with perceptually matched foils allowed us to dissociate more general, or gist-based memories (e.g., object was paired with a beach) versus specific associative memories (e.g., object was paired with *that* beach). Questions were separated by an ISI of 0.5 s. Choosing the correct, specific scene from encoding denoted correct associative memory.

Task stimuli

Objects. A total of 400 photographs of emotional alcohol and neutral handheld stimuli were obtained from prior studies (Dunsmoor et al., 2012; Van Der Linden et al., 2015; Fey et al., 2017; Sinha et al., 2022) and from Google image searches. All images were edited to appear on a gray background with visible text occluded and were resized to 250×250 pixels. Images were chosen to be perceptually distinct from one another and were evenly distributed into four subcategories (alcohol: beer, wine, liquor, and mixed drinks; neutral: items likely to be found in a kitchen, garage, bathroom, and office). A separate validation experiment was conducted to rate a large corpus of images ($N = 400$ photographs). They first rated each image's emotional salience using the Self-Assessment Manikin image scale (Bradley and Lang, 1994) to rate valence (1 = "unhappy" to 5 = "happy") and arousal (1 = "calm" to 5 = "excited"). Participants additionally provided ratings of craving ("How much do you want to drink?" 1 = "none at all" to 5 = "a great deal"). They then rated each image on perceptual features of detail ("How detailed is this picture?", 1 = "very simple" to 5 = "very complex") (Dager et al., 2014) and familiarity ("Do you recognize this item?", 1 = "very unfamiliar" to 5 = "very familiar") (Bainbridge et al., 2017).

This validation experiment confirmed that the alcohol images were rated as significantly more emotionally arousing than household objects. For each participant, a subset ($N = 160$/wk; 80 encoded and 80 foils) of these images were pseudorandomly selected such that perceptual and affective features did not significantly differ between weeks. This randomization process ensured that the chosen images were matched across participants, without enforcing that all participants saw the same subset of images (thus reducing the likelihood of bias in the stimulus set producing spurious results). Although the full set of emotional objects were rated as significantly more detailed and less familiar than neutral objects in the validation experiment, these ratings did not predict memory for object/scene pairs, nor did they significantly interact with pill or block to modulate memory. All reported memory and hippocampal effects remained significant when including these ratings in statistical models.

Scenes. A total of 320 indoor and outdoor scene images were obtained from the SUN database (Xiao et al., 2010) and Google Image searches. Specifically, we obtained 80 indoor and 80 outdoor scene images, each with a same scene-type perceptual match (e.g., two pictures of beaches) that served as a foil during the associative memory test. As with object stimuli, a separate validation sample was collected to confirm that perceptual similarity between old and foil images was matched for emotional and neutral object pairmates. Specifically, participants in the validation experiment were shown sets of pairmates and asked to rate how similar they were on a scale of 0 (not at all similar) to 100 (very similar). These scenes were randomly paired with emotional or neutral objects per week per participant so that similarity did not differ between weeks or between blocks.

Hydrocortisone administration and cortisol measurement

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

Pill administration. Across the two encoding sessions, participants received one oral tablet of hydrocortisone 20 mg and one oral tablet of placebo (sucrose). The two pills were physically identical. The order of pill administration (week 1 or 2) was counterbalanced by an unblinded statistician, with all additional experimental personnel and participants blinded for the duration of the study. Pills were compounded by the Yale Investigational Drug Service and stored at 20°C-25°C. Pills were administered ~1 h before the start of the first encoding run, to allow for pharmacokinetics and pill metabolism, targeting significant elevations in central cortisol levels at the time of encoding (consistent with Buchanan and Lovallo, 2001; Rimmele et al., 2003).

Measuring salivary cortisol levels. Participants provided six saliva samples over the two fMRI sessions (three per session) to measure cortisol concentration. The baseline sample was obtained ~10 min after arrival (after acclimation to the environment and before pill administration). The encoding sample was obtained immediately before the first encoding run, ~1 h after pill administration. The final sample was obtained after participants exited the scanner. Samples were collected using Starstedt Salivate Tubes and samples were processed by the Yale Center for Clinical Investigation using radioimmunoassay.

Measuring awareness. To measure subjective awareness of pill administration, participants reported which pill they thought they had received during each encoding session (response options: Cortisol, Placebo, or Not Sure). Participants were asked immediately after consuming the pill and after the fMRI scan.

To measure potential pill-induced changes in subjective affect, participants completed the PANAS shortly after arrival at the scanning center, and again immediately after exiting the scanner (after encoding).

fMRI procedure

Participants underwent fMRI scanning after each pill administration. Specifically, participants performed the encoding task (described above) while BOLD fMRI data were acquired. We additionally collected a localizer run and resting-state fMRI scans.

Localizer run. Before encoding, participants completed a 6 min run in which they viewed images (1 s each, 0.5 s intertrial interval) and were instructed to button press anytime an image repeated twice in a row (1-back). They viewed 8 blocks of 22 images each. The blocks consisted of scenes, emotional alcoholic beverages, neutral handheld objects, or phase-scrambled versions of the alcohol and neutral images. None of these images was repeated in the subsequent encoding task. Each category appeared twice during the 8 blocks in a randomized order per subject.

Rest runs. Participants underwent three 6 min rest scans throughout each session: one before encoding (after the localizer run) and one immediately after each encoding run. No data from these rest runs are reported in the current paper.

MRI acquisition parameters

Data were acquired on Siemens 3T Prisma scanners using a 64-channel coil at the Magnetic Resonance Research Center at Yale University. Data were acquired across three scanners ($N = 4$ on Scanner A, $N = 2$ on Scanner B, $N = 21$ on Scanner C). Parameters were the same across

scanners. Importantly, each participant completed both of their MRI sessions on the same scanner, and control analyses revealed no effect of scanner on our variables of interest.

Functional images were acquired using an EPI sequence with the following parameters: TR = 1000 ms, TE = 30 ms, 75 axial slices, voxel size = 2 × 2 × 2 mm, flip angle = 55 degrees, multiband factor = 5, interleaved acquisition, FOV: 220 × 220.

Anatomical data were acquired using one T1-weighted 3D MPRAGE sequence (TR = 2400 ms, TE = 1.22 ms, 208 sagittal slices, voxel size = 1 × 1 × 1 mm, flip angle = 8 degrees, FOV: 256 × 256) and one T2-weighted turbo spin echo (TR = 11,170 ms, TE = 93 ms, 54 coronal slices, voxel size = 0.44 × 0.44 × 1.5 mm, distance factor = 20%, flip angle = 150 degrees).

Quantification and statistical analysis

fMRI preprocessing. fMRI data were preprocessed using FSL 6.0.1. All encoding runs met criteria for inclusion based on motion (defined *a priori* as <1.5 mm absolute mean frame-to-frame displacement, as computed by FSL's MCLFIRT) (Jenkinson et al., 2002). Data were skull-stripped (BET) (Smith, 2002), prewhitened (FILM) (Woolrich et al., 2001), and high-pass filtered at 0.01 Hz to remove low-frequency signal drift. We then used FSL's FEAT (http://www.fmrib.ox.ac.uk/fsl) to run a GLM per run to control for motion and covariates of no interest. Regressors included 6 linear estimated motion parameters and white matter time-series (each plus temporal derivatives) and stick function regressors for nonlinear motion outliers. No smoothing was applied.

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

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

ROI definition. Hippocampal subfields and medial temporal lobe cortical regions were defined individually for each participant primarily based on their T2-weighted anatomic images. Segmentation was done automatically (using both the T1- and T2-weighted anatomic images) using the automated segmentation of hippocampus subfields software package (Yushkevich et al., 2015). We used an atlas containing 51 manual segmentations of hippocampal subfields (Aly and Turk-Browne, 2016a,b). The automated segmentations were visually inspected for quality assurance and in 4 cases when automatic segmentation was particularly poor, manual segmentation was performed. Manual segmentation was performed using the procedure (i.e., using the same anatomic landmarks) as the segmentations which comprised the atlas (Insausti et al., 1998; Pruessner et al., 2002; Duvernoy, 2005), as described in detail in Aly and Turk-Browne (2016b). The hippocampus was segmented into CA1, CA2/3, dentate gyrus (DG), and subiculum subfields; medial temporal lobe cortex was segmented into entorhinal cortex (EC), perirhinal cortex, and parahippocampal cortex. All ROIs were defined separately in each hemisphere, and then concatenated together to generate bilateral ROIs. For analysis purposes, the CA2/3 and DG subfields were concatenated into a single CA23DG subfield. Further, a whole hippocampus ROI was constructed by concatenating the CA23DG, CA1, and subiculum ROIs. One participant did not have a high-resolution T2-weighted image; and thus, their hippocampal subfields could not be segmented; this participant was excluded from all neural analysis looking at the hippocampus. Although the segmentation protocol resulted in segmentations for all hippocampal and medial temporal lobe cortex subfields, we did not perform any analyses on the perirhinal cortex, parahippocampal cortex, or subiculum ROIs (though as noted above, the subiculum ROI was included when generating the whole hippocampus ROI).

In addition to MTL ROIs, we analyzed data from amygdala and lateral occipital cortex (LOC). Anatomical amygdala ROIs were defined for each participant based on their T1 MPRAGE scans using FSL's FIRST automated segmentation tool (Patenaude et al., 2011). As with the MTL ROIs, amygdala ROIs were defined in each hemisphere and concatenated together to generate a single bilateral amygdala ROI.

LOC ROIs were functionally defined based on the localizer scan. These data were preprocessed as described above for encoding runs; then residuals were smoothed (6 mm FWHM) and entered into subject-level GLMs to extract β values per block type (emotional objects, neutral objects, scenes, and phase-scrambled images). These subject-level estimates were aligned to MNI space and entered into a group-level ANOVA (AFNI's 3dANOVA3) as a function of pill and image type. LOC was then defined at the group level from a *post hoc* contrast of neutral objects versus scrambled images, cluster-corrected ($p < 0.001$, $\alpha = 0.05$, AFNI's 3dClustSim) and then masked with the Harvard-Oxford Probabilistic Atlas definition for LOC (50% threshold). This mask was then aligned to each participant's functional data. Although this procedure was not constrained by hemisphere, the resulting mask was bilateral.

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

Representational similarity analysis. To probe the representational content of encoded associations, 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 and time (5 TRs during which the object-scene pair was on screen). To account for the hemodynamic lag, we shifted the data by 5 s (5 TRs), such that the extracted pattern reflected the BOLD activity 5-10 s after 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 averaged correlations via Fisher r-to-z transform.

Univariate subsequent memory analysis. 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 smoothed the residuals from the preprocessing models above (6 mm FWHM) and then ran a separate GLM 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 of 5 s), convolved with a double-γ HRF. We then computed the contrast between subsequently remembered and subsequently forgotten associations. For each ROI, we extracted these contrast estimates averaged across voxels within the ROI, separately for each block and pill. We refer to this difference as the "subsequent memory effect."

Statistical modeling

All statistical analyses were conducted as linear mixed effect models and were performed in R (version 4.1.3) using the nlme package (Pinheiro et al., 2022).

Analyses primarily assessed the effects of block (Emotional alcoholic beverages vs Neutral household objects) and pill (cortisol vs placebo), as well as the interactions between the two, on various behavioral and neural outcome measures. To account for possible effects of block order (Emotional first vs Neutral first), pill order (Cortisol first vs Placebo first), and week (given that at the second week, participants were more familiar with the experimental procedures), we included these factors as covariates in all analyses, where relevant. That is, for analyses that examined the effects of block and pill, we modeled the effect of interest as a function of block, pill, and the block × pill interaction, followed by covariates of week, pill order, and block order. For analyses that examined a difference between cortisol and placebo, we included covariates of pill order and block order (week is redundant with pill order here, given the nature of the difference score). We included these covariates only as main effects (i.e., we did not model their interactions with any of the

effects of interest); we opted for this approach to simplify the interpretability of the models, given that we did not have hypotheses about how these covariates would interact with our effects of interest. All models treated participant as a random effect, such that a random intercept was computed for each participant. We did not include random slopes for any effects, although we note that including random slopes renders qualitatively equivalent — if anything, stronger — results.

Given our focus on a small subset of ROIs (with our primary focus being on hippocampal subfields CA1 and CA2/3/DG), we did not correct for multiple comparisons when interpreting model results. To reduce the total number of comparisons being performed, we limited all brain–behavior relationships only to ROIs for which there was a main effect of pill and/or block on the neural measure of interest.

When relevant, follow-up tests to linear mixed effects models 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 versus forgotten contrasts differed from 0. Pairwise comparisons were performed with emmeans adjusted for multiple comparisons using the Tukey HSD method.

Results

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

To validate the efficacy of the hydrocortisone tablet administration, we collected salivary samples throughout the scan session (Fig. 1*D*). Indeed, participants exhibited elevated salivary cortisol following drug, but not placebo (Fig. 1*E*); the observed post-pill salivary cortisol concentrations are comparable to what was obtained in prior work using similar dosages and timing (Buchanan and Lovallo, 2001; Rimmele et al., 2003). We observed main effects of pill $[F(1, 118) = 35.12, p < 0.001,\ \eta_p^2 = 0.20]$ and time point $[F(2, 118) = 7.27, p = 0.001,\ \eta_p^2 = 0.093]$, as well as a pill × time point interaction $[F(2, 118) = 9.38, p < 0.001,\ \eta_p^2 = 0.12]$. Importantly, drug-induced cortisol was significantly higher than placebo at both the pre- and post-encoding time points (p values < 0.001), indicating that cortisol levels remained elevated throughout encoding.

Despite this robust increase in peripheral cortisol, we did not observe significant changes in awareness or overall affect. Overall, participants were unaware of which pill they had received (immediately post-pill: 9% correct, 74% unsure, 17% incorrect; post-scan: 29% correct, 45% unsure, 26% incorrect). Furthermore, we found no significant changes in positive $[F(1, 23) = 0.81, p = 0.38,\ \eta_p^2 = 0.017]$ or negative $[F(1, 23) = 1.39, p = 0.25,\ \eta_p^2 = 0.039]$ affect, as measured by the difference in PANAS scores measured pre- and post-scan.

Hydrocortisone modulates subjective affect at encoding

After pill administration, participants completed two runs of an associative memory encoding task while undergoing fMRI (Fig. 1*A*, left). Participants encoded associations between neutral scenes and either handheld, household objects (Neutral block) or alcohol-related objects (Emotional block). They were instructed to vividly imagine each object and scene interacting and then rate whether the imagined interaction was happy, neutral, or unhappy (valence rating) and how intensely they felt that way (arousal rating; Fig. 1*B*) (Goldfarb et al., 2019, 2020).

Hydrocortisone did not influence arousal ratings $[F(1, 75) = 0.37, p = 0.54,\ \eta_p^2 = 0.005]$. There was a main effect of block (Emotional [alcohol] vs Neutral [household] objects) $[F(1, 75) = 6.27, p = 0.015,\ \eta_p^2 = 0.075]$; consistent with the stimulus design, participants rated emotional associations as more arousing than the neutral associations (Fig. 2*A*). However, this stimulus-linked arousal was not modulated by hydrocortisone (pill × block: $[F(1, 75) = 0.64, p = 0.43,\ \eta_p^2 = 0.008]$).

In contrast, hydrocortisone did modulate valence ratings (Fig. 2*B*). Examining the proportion of trials rated as "happy," "neutral," or "unhappy" revealed a main effect of valence $[F(2, 281) = 95.73, p < 0.001,\ \eta_p^2 = 0.39]$, such that the majority of trials were rated as neutral. There was no interaction between block and valence $[F(3, 281) = 1.69, p = 0.17,\ \eta_p^2 = 0.016]$, indicating that the relative proportions of trials rated as happy, neutral, and unhappy did not differ across the Emotional and Neutral blocks. Although there was no main effect of pill $[F(1, 281) = 0.063, p = 0.80,\ \eta_p^2 = 0.00]$, there was a significant valence × pill interaction $[F(2, 281) = 3.56, p = 0.030,\ \eta_p^2 = 0.023]$. This interaction was driven by a smaller proportion of trials rated as "neutral" under hydrocortisone relative to placebo ($\beta = -0.082$[SE 0.036]; $t_{(281)} = -2.29, p = 0.023$). Although this reflected a numerical shift toward increased ratings of both "happy" and "unhappy" under hydrocortisone, neither of these pairwise comparisons reached significance (happy: $\beta = 0.020[0.036]$; $t_{(281)} = 0.54$, $p = 0.58$; unhappy: $\beta = 0.046$[SE 0.036]; $t_{(281)} = 1.28, p = 0.20$). That is, hydrocortisone amplified emotional salience at encoding by shifting participants' valence ratings broadly away from neutral and toward feeling more positive or negative about encoded associations.

Together, these results suggest that hydrocortisone may modulate participants' subjective valence (shifting them away from neutral and toward positive or negative) without affecting participants' subjective arousal. Although we treat subjective valence and arousal as separate outcome measures, it is worth noting that the two responses may be conceptually related insofar as participants first rated subjective valence (how they felt), followed by arousal (how intensely they felt that way). Thus, we analyzed arousal conditional on valence to assess whether taking valence into account might reveal an effect of hydrocortisone on arousal. The patterns reported above held even when examining arousal separately by valence. That is, binning arousal by valence ("happy," "unhappy," "neutral") revealed a main effect of valence on arousal ratings $[F(2, 258) = 49.1, p < 0.001,\ \eta_p^2 = 0.27]$. As might be expected, arousal ratings were higher for trials rated as both "happy" and "unhappy," relative to "neutral" (happy vs neutral: $\beta = 0.63[0.063]$; $t_{(258)} = 9.91, p < 0.001$; unhappy vs neutral: $\beta = 0.29[0.066]$; $t_{(258)} = 4.40, p < 0.001$). Trials rated as "happy" were also rated as significantly more arousing than "unhappy" trials ($\beta = 0.34[0.066]$; $t_{(258)} = 5.06$, $p < 0.001$). However, including valence did not reveal a main effect of pill, nor interactions among pill, valence, and block (p values > 0.30).

Hydrocortisone alters the relationship between arousal and associative memory encoding

Participants were tested on their memory for encoded associations 24 h later. On each trial, participants viewed an object and were asked to select which of four scenes was paired with the object at encoding (Fig. 1*C*). Participants selected the correctly paired scene more often than chance (chance = 0.25; mean proportion correct = 0.36, SD = 0.094). Performance did not differ as a function of pill $[F(1, 75) = 0.25, p = 0.62,\ \eta_p^2 = 0.003]$, although it did differ by block $[F(1, 75) = 8.23, p = 0.0054,\ \eta_p^2 = 0.092]$, with better memory for neutral associations (Fig. 2*C*). Hydrocortisone also did not modulate participants' likelihood of choosing the perceptually matched lure scene $[F(1, 75) = 0.13, p = 0.72,\ \eta_p^2 = 0.002]$.

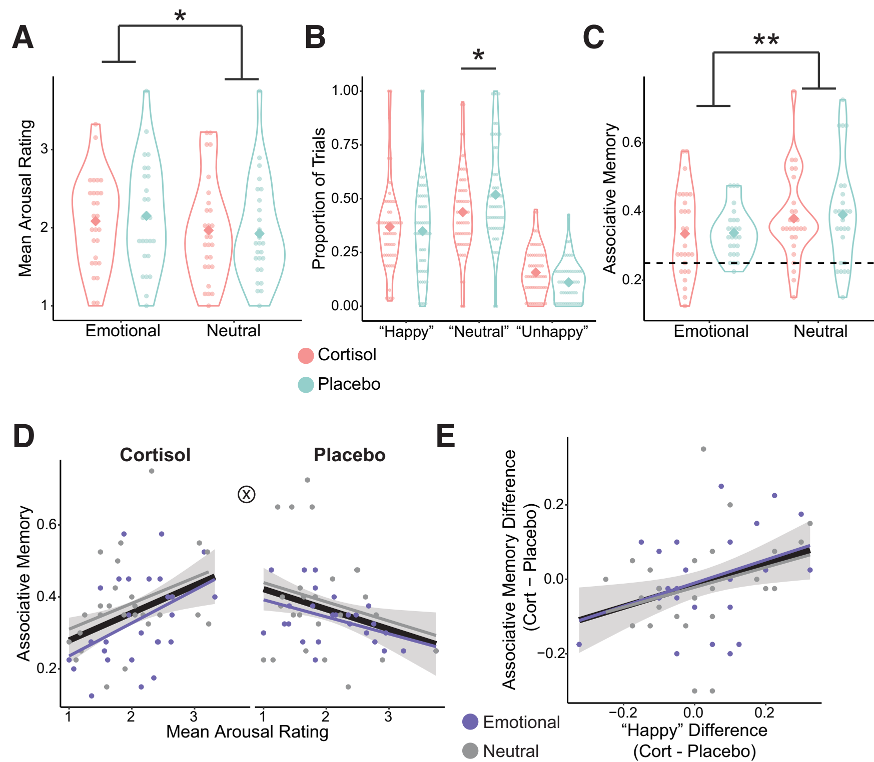

Figure 2. Behavioral results. ***A***, Participants rated emotional associations as more arousing than neutral associations. ***B***, Cortisol altered the valence of encoded associations, such that participants were less likely to endorse feeling "neutral" about the object-scene pair. ***C***, Participants performed above chance (0.25; 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***, Small dots represent individual participants. Larger diamonds represent mean across participants. ***D***, ***E***, Each dot represents an individual participant. Error shading represents 95% CI around the line of best fit, collapsed across blocks (black line). Individual colored lines indicate the line of best fit within each block. $^{*}p < 0.05$. $^{**}p < 0.01$.

Prior work has demonstrated that subjective affect can modulate cortisol effects on memory (Abercrombie et al., 2003). Thus, we examined whether memory was affected by subjective arousal differently under hydrocortisone versus placebo. Indeed, arousal and pill interacted $[F(1, 71) = 9.30, p = 0.0032,\ \eta_p^2 = 0.11]$. Participants with higher subjective arousal under hydrocortisone had better associative memory for trials encoded under hydrocortisone, whereas higher subjective arousal under placebo predicted worse associative memory under placebo (Fig. 2*D*). This difference was significant for both emotional [$\beta = 0.080[0.40]$; $t_{(71)} = 2.01$, $p = 0.048$] and neutral [$\beta = 0.095[0.038]$; $t_{(71)} = 2.48$, $p = 0.016$] blocks.

As hydrocortisone modulated valence ratings during encoding, such that participants shifted away from feeling "neutral" under hydrocortisone, we asked whether shifts toward happy or unhappy judgments were related to later associative memory. To account for this effect of hydrocortisone, we thus ran this analysis using difference scores (predicting the difference in memory between hydrocortisone and placebo from the difference in ratings between hydrocortisone and placebo). Indeed, the change in subjective "happy" ratings predicted the change in associative memory from placebo to hydrocortisone across participants, $[F(1, 23) = 6.22, p = 0.020,\ \eta_p^2 = 0.12]$, with more "happy" ratings under hydrocortisone corresponding to better memory (Fig. 2*E*). This effect did not interact with block $[F(1, 23) = 0.0070, p = 0.93,\ \eta_p^2 = 0.00]$. Because this analysis differs from the other reported analyses in that it examines differences from hydrocortisone to placebo, we also analyzed the data separately by pill. The observed pattern was driven by a positive relationship between valence ratings and memory under hydrocortisone [$\beta = 0.23[0.078]$; $t_{(71)} = 2.93$, $p = 0.0045$]; in contrast, there was no relationship between valence and memory under placebo [$\beta = 0.078[0.074]$; $t_{(71)} = 1.06$, $p = 0.29$; difference between hydrocortisone and placebo: $t_{(71)} = 1.84$, $p = 0.070$]. Last, this effect was specific to positive valence; the change in "unhappy" ratings did not predict differences in associative memory for either block across participants [Main effect of rating: $F(1, 23) = 0.36, p = 0.56,\ \eta_p^2 = 0.008$; rating × block interaction: $F(1, 23) = 0.33, p = 0.57,\ \eta_p^2 = 0.007$].

To probe whether valence or arousal primarily modulated hydrocortisone effects on associative memory (and to account for the staged rating scheme, in which participants first reported valence, then arousal), we separated data by valence ratings and computed memory and arousal per self-reported valence category. Analyzing the data in this way replicated the pill × arousal interaction on memory $[F(1, 246) = 8.93, p = 0.0031,\ \eta_p^2 = 0.034]$; arousal and valence did not interact, nor was there a three-way interaction between arousal, valence, and pill (p values > 0.20). This finding suggests that arousal broadly (regardless of valence) alters the relationship between hydrocortisone and associative memory.

Although our primary analyses focused on associative memory for object-scene pairs, we observed similar patterns for item-level recognition of individual objects. We quantified item memory for each participant by computing d' from participants' responses on the Object Recognition Task, in which they had to indicate whether an object was present during encoding or not. d' is a measure that takes into account a participant's hit rate

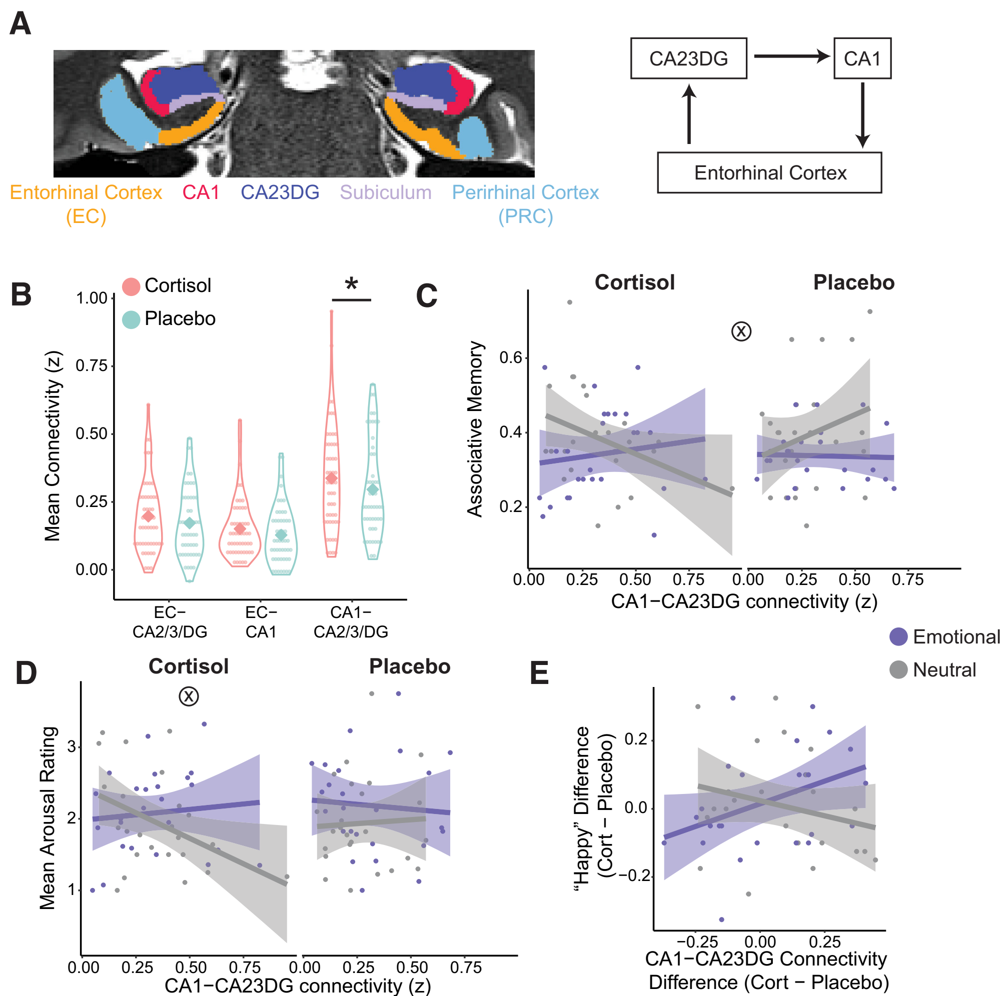

Figure 3. Background connectivity results. ***A***, Left, Example hippocampal and medial temporal lobe subfields on a representative participant. Right, Schematic of hippocampal trisynaptic pathway. ***B***, Hydrocortisone led to increased background connectivity between hippocampal subregions. ***C***, CA1-CA23DG connectivity interacted with pill and block 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***, Small dots represent individual participants. Larger diamonds represent mean across participants. $^{*}p < 0.05$. ***C–E***, Error shading represents 95% CI around the best fit line.

(proportion of trials in which participants correctly identified an object as from encoding) and false alarm rate (proportion of trials in which participants incorrectly endorsed a foil object as being from encoding), such that higher d' values indicate a greater separation between hits and false alarms. There was a main effect of block on d' $[F(1,75) = 10.60, p = 0.0017,\ \eta_p^2 = 0.12]$, such that participants had better recognition memory for neutral objects, but no main effect of pill $[F(1,75) = 0.012, p = 0.91,\ \eta_p^2 = 0.00]$. We also found an interaction between arousal and pill $[F(1,71) = 10.36, p = 0.0019,\ \eta_p^2 = 0.12]$, such that, under hydrocortisone, participants with higher subjective arousal had better object recognition memory, whereas under placebo, participants with higher subjective arousal had worse object recognition memory. Last, the change in participants' subjective "happy" ratings predicted the difference in memory performance from hydrocortisone to placebo, $[F(1,23) = 12.08, p = 0.0020,\ \eta_p^2 = 0.25]$, with more "happy" ratings under hydrocortisone corresponding to better recognition memory (higher d').

Together, these data demonstrate that subjective affect modulates hydrocortisone effects on encoding. Subjective arousal and positive affect bolstered memories encoded with elevated cortisol, but impaired memories under placebo.

Hydrocortisone enhances intrahippocampal connectivity to promote emotional associative memory

After establishing that hydrocortisone interacts with subjective arousal to promote memory, we next investigated whether hippocampal mechanisms could support these memory enhancements. We first examined whether intrahippocampal connectivity was modulated by hydrocortisone. The hippocampus contains multiple subfields connected to EC, the primary input/output region for the hippocampus (Fig. 3A, left). Information from EC is relayed to CA3/DG, which then connects to CA1; CA1 then communicates back out to EC (Fig. 3A, right). This circuit (known as the trisynaptic pathway) is particularly important for episodic memory encoding given the sparse connections and high inhibition in CA3 and DG that enable pattern separation (Schapiro et al., 2017). We performed a background connectivity analysis (Al-Aidroos et al., 2012) to examine how BOLD responses throughout the hippocampal circuit cofluctuate during encoding following hydrocortisone. Although we ran this analysis for all edges of our simplified hippocampus circuit (EC-CA23DG, CA1-CA23DG, and CA1-EC), we were particularly interested in the CA1-CA23DG edge, as this directly probes hydrocortisone effects on the hippocampus.

Hydrocortisone enhanced connectivity between CA1 and CA23DG [$F(1, 72) = 5.20, p = 0.026,\ \eta_p^2 = 0.064$]. Although this effect was only reliable for CA1-CA23DG, follow-up analyses revealed that it was in the same direction for EC-CA23DG [$F(1, 72) = 2.01, p = 0.16,\ \eta_p^2 = 0.026$] and EC-CA1 [$F(1, 72) = 2.38, p = 0.13,\ p^2 = 0.030$ as well (Fig. 3*B*)]. Connectivity did not differ between blocks (main effect and cortisol interaction: p values > 0.40). These data suggest that cortisol potentiates intrahippocampal communication.

Because prior work has suggested that stress can alter hippocampal–amygdala connectivity (e.g., Vaisvaser et al., 2013), we next examined whether cortisol altered connectivity between the amygdala and the hippocampal circuit. Hydrocortisone was associated with a marginal decrease in amygdala-EC connectivity [$F(1, 72) = 3.03, p = 0.086,\ \eta_p^2 = 0.038$] but had no significant effect on amygdala-CA1 [$F(1, 72) = 2.21, p = 0.14,\ \eta_p^2 = 0.029$] or amygdala-CA23DG connectivity [$F(1, 72) = 0.41, p = 0.53,\ \eta_p^2 = 0.005$]. As with intrahippocampal connectivity, amygdala-hippocampal connectivity did not differ between blocks (main effect and cortisol interaction: p values > 0.30).

Given that intrahippocampal, but not amygdala-hippocampal, connectivity was modulated by hydrocortisone, we next tested how intrahippocampal connectivity related to subsequent associative memory. We observed a three-way interaction between CA1-CA23DG connectivity, block, and pill, $F(1, 68) = 4.92, p = 0.030,\ \eta_p^2 = 0.062$ (Fig. 3*C*). Under placebo, greater intrahippocampal connectivity was associated with stronger associative memory, as would be expected from neural network models (Schapiro et al., 2017). This facilitation did not differ between blocks [$\beta = -0.16[0.15]$; $t_{(68)} = -1.05$, $p = 0.30$]. However, following hydrocortisone, this relationship changed: with higher intrahippocampal connectivity, emotional, rather than neutral, associations were preferentially remembered (emotional vs neutral: $\beta = 0.28[0.13]$; $t_{(68)} = 2.14$, $p = 0.036$).

This finding suggests a reprioritization of hippocampal connectivity to promote emotional, rather than neutral, memories under hydrocortisone. To probe whether this relationship was driven by emotionality, we assessed whether hippocampal connectivity under hydrocortisone also tracked subjective arousal (Fig. 3*D*). Indeed, we observed a significant interaction between connectivity and block under hydrocortisone [$F(1, 23) = 6.54$, $p = 0.018,\ \eta_p^2 = 0.21$]. Mirroring the relationship between connectivity and associative memory, hippocampal connectivity positively tracked arousal for emotional, but not neutral, associations. In contrast, subjective arousal was not related to connectivity under placebo (p values > 0.50), although we note that the three-way interaction between connectivity, block, and pill was not statistically significant [$F(1, 68) = 2.03, p = 0.16,\ \eta_p^2 = 0.028$].

Notably, intrahippocampal connectivity tracks both associative memory and subjective arousal under hydrocortisone. As these two effects were related behaviorally (with subjective arousal predicting associative memory), we next ran targeted model comparisons to understand whether associative memory and arousal contribute independent variance to intrahippocampal connectivity under hydrocortisone. We found that removing the arousal × block interaction significantly decreased the fit of the model $\chi^2_{(1)} = 4.51$, $p = 0.034$, whereas removing the memory × block interaction did not significantly alter the fit of the model $\chi^2_{(1)} = 0.94$, $p = 0.33$, thereby suggesting that the relationship between connectivity and associative memory under cortisol may be in part explained by arousal.

We next assessed whether intrahippocampal connectivity tracked subjective valence. Behaviorally, we had observed that hydrocortisone-induced shifts in positive affect related to better associative memory. To assess whether this affective dynamic was related to intrahippocampal connectivity, we again computed difference scores to assess whether hydrocortisone-associated changes in connectivity related to changes in valence ratings. Although this relationship was not as strong as observed with arousal, we did find a marginal interaction between changes in CA1-CA23DG connectivity and changes in positive affect (connectivity × block: [$F(1, 22) = 4.25, p = 0.051,\ \eta_p^2 = 0.11$]). Connectivity changes were positively associated with the change in "happy" ratings for emotional, but not neutral trials (Fig. 3*E*). Examining the relationship between happiness ratings and CA1-CA23DG connectivity separately for each pill (rather than computing a difference score) suggested that the block interaction may have been driven by changes because of hydrocortisone: Under cortisol, connectivity differentially predicted happiness ratings for Emotional versus Neutral blocks [$\beta = 0.43[0.18]$; $t_{(68)} = 2.43$, $p = 0.018$], whereas under placebo, the relationship between connectivity and happiness ratings did not differ by block [$\beta = 0.071[0.21]$; $t_{(68)} = 0.34$, $p = 0.74$].

Together, these data suggest an intrahippocampal mechanism supporting cortisol-induced enhancement of emotional memories. Under placebo, CA1-CA23DG connectivity predicted episodic memory for neutral associations, but this relationship shifted with hydrocortisone, with CA1-CA23DG connectivity selectively predicting emotional associative memory. CA1-CA23DG connectivity also tracked aspects of subjective affect that modulate hydrocortisone effects on associative memory, thereby providing an intrahippocampal explanation for positive effects of hydrocortisone on emotionally arousing, positively valenced memories.

Hydrocortisone reverses the relationship between hippocampal pattern similarity and associative memory

The connectivity approach above allowed us to examine how hydrocortisone modulates cofluctuations in univariate activity in intrahippocampal and hippocampal–amygdala circuits. However, the representational content housed in these regions remains unclear. Prior work using multivariate pattern analysis of hippocampal activity demonstrated that representational distinctiveness, particularly in CA23DG, supports episodic memory encoding (LaRocque et al., 2013; Wanjia et al., 2021). This dissimilarity is computationally important, as minimizing overlap between neural patterns associated with similar memories allows those memories to be encoded distinctly, without interference from one another (Favila et al., 2016; Chanales et al., 2017). Further, recent work has demonstrated that acute stress promotes representational similarity in the amygdala (Bierbrauer et al., 2021). Thus, we next explored the effects of hydrocortisone on representations within the hippocampal circuit and amygdala during encoding. We examined within-run pattern similarity, a metric of how similar the neural pattern for an encoded association is to all other associations within that run (Fig. 4*A*).

Hydrocortisone did not significantly affect within-run pattern similarity in CA1 [$F(1, 72) = 1.21, p = 0.27,\ \eta_p^2 = 0.013$], CA23DG [$F(1, 72) = 0.36, p = 0.55,\ \eta_p^2 = 0.004$], EC [$F(1, 72) = 3.69, p = 0.059,\ \eta_p^2 = 0.037$], or amygdala [$F(1, 75) = 0.22, p = 0.64,\ \eta_p^2 = 0.003$]. However, block did modulate CA23DG similarity [$F(1, 72) = 4.86, p = 0.031,\ \eta_p^2 = 0.054$], with relatively greater pattern similarity for emotional, relative to neutral associations (Fig. 4*B*); this was not true in CA1 or EC (p values > 0.20). To ensure that this difference was not because of visual content (i.e., greater inherent visual similarity among emotional

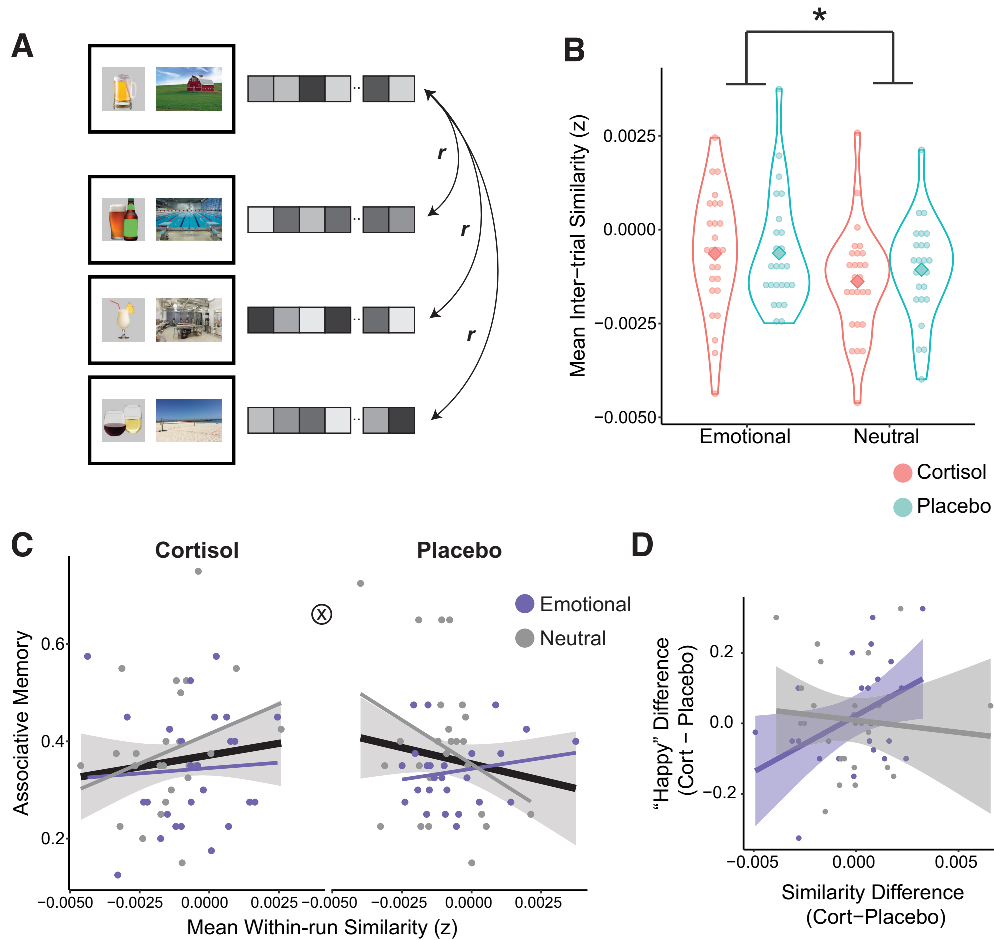

Figure 4. Within-run pattern similarity results. ***A***, We extracted the spatiotemporal pattern associated with each encoding trial. We then correlated each trial to all other trials (averaging the correlations across trials) to obtain a global pattern similarity metric. ***B***, CA23DG pattern similarity differed by block, 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***, Small dots represent individual participants. Larger diamonds represent mean across participants. $^{*}p < 0.05$. ***C***, ***D***, Error shading represents 95% CI around the best fit line. Individual colored lines indicate the line of best fit within each block.

objects), we also examined pattern similarity in LOC, an object-sensitive visual region. There was no effect of either pill $[F(1,75) = 0.01, p = 0.94, \eta_p^2 = 0.00]$ or block $[F(1,75) = 0.51, p = 0.48, \eta_p^2 = 0.007]$ on LOC similarity, suggesting that the block differences in CA23DG were not driven by visual similarity. These block differences were also not observed in amygdala $[F(1,75) = 0.47, p = 0.50, \eta_p^2 = 0.005]$.

Given that CA23DG similarity was modulated by block, we next explored whether variance in CA23DG similarity related to associative memory performance. Although there was no overall pill effect on pattern similarity, the relationship between CA23DG similarity and subsequent associative memory did differ with hydrocortisone (Fig. 4C). Specifically, we observed a similarity by pill interaction $[F(1,68) = 5.46, p = 0.022, \eta_p^2 = 0.069]$, as well as a marginal three-way interaction among similarity, pill, and block $[F(1,68) = 3.40, p = 0.070, \eta_p^2 = 0.044]$. Whereas CA23DG similarity negatively predicted memory under placebo (consistent with more distinct neural representations supporting more precise memories), it positively predicted memory under hydrocortisone $[\beta = 32.2[12.7]; t_{(68)} = 2.53, p = 0.014]$.

Given that associative memory related to subjective affect, we next examined whether CA23DG similarity predicted arousal or the change in affect ratings. There were no reliable associations between similarity and arousal (p values > 0.10). However, CA23DG similarity did relate to the cortisol-induced shift toward positive valence. Increased CA23DG similarity with hydrocortisone tracked increased happiness ratings with hydrocortisone for emotional, but not neutral, associations $[F(1,22) = 5.14, p = 0.034, \eta_p^2 = 0.13$; Fig. 4D]. The relationship between similarity and happiness ratings was numerically positive for both Emotional and Neutral under hydrocortisone: [Emotional vs Neutral: $\beta = 9.81[24.3]; t_{(68)} = 0.41, p = 0.69$]. However, under placebo, the relationship between similarity and happiness rating differed by block $[\beta = 59.24[28.0]; t_{(68)} = 2.11, p = 0.038]$.

Together, these data suggest that hydrocortisone reverses the relationship between neural similarity and associative memory. Consistent with prior work (e.g., LaRocque et al., 2013), CA23DG similarity negatively predicted memory under placebo; this may reflect the computational need for episodic memory to separate memories encoded in a similar temporal context, to reduce interference across those memories at test. Intriguingly, however, we observed a positive relationship between similarity and associative memory under cortisol, suggesting that cortisol may lead memories to be encoded in a fundamentally different, integrated fashion. Relatively greater pattern similarity was also associated with increased "happy" ratings under cortisol, but this effect was specific to emotional associations. Together, these

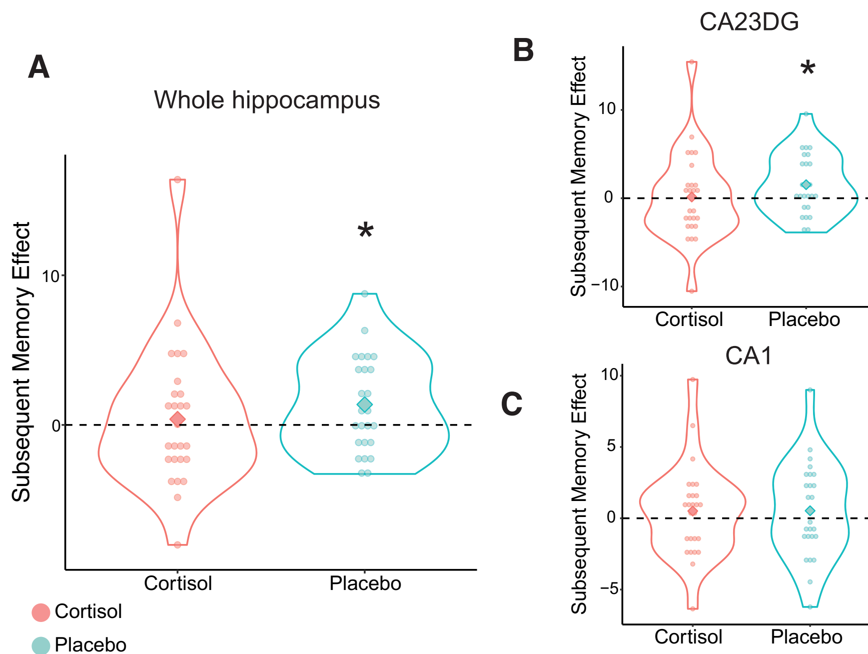

Figure 5. Hippocampal subsequent memory effects. ***A***, Univariate subsequent memory effect (difference in encoding activation for subsequently remembered, vs forgotten trials), averaged across all voxels in the hippocampus. ***B***, Subsequent memory effect in CA23DG. ***C***, Subsequent memory effect in CA1. Small dots represent individual participants. Larger diamonds represent mean across participants. $^*p < 0.05$.

results suggest a distinct hippocampal mechanism for promoting emotional memories under cortisol.

Hydrocortisone blunts hippocampal subsequent memory effects

Our primary interest in the current study was understanding how intrahippocampal dynamics (including functional coupling and representational content) change with hydrocortisone and contribute to later memory. However, prior work has focused on univariate hippocampal effects, including demonstrating stress and cortisol-induced impairment via hippocampal subsequent memory effects (i.e., the difference between hippocampal activity for later remembered vs forgotten items) (Henckens et al., 2009; Qin et al., 2012). Thus, to facilitate comparison with this prior work highlighting negative stress effects on hippocampal memory processes, we ran GLMs contrasting subsequently remembered versus forgotten associations in the hippocampus (separately for each participant, pill, and block).

In the whole hippocampus, there was no main effect of pill or block, nor an interaction between the two (p values > 0.30). Collapsing across blocks revealed a reliable subsequent memory effect under placebo [mean difference = 1.36; SD = 3.24; $t_{(24)} = 2.10$, $p = 0.046$, $d = 0.42$], consistent with prior work (e.g., Davachi et al., 2003) (Fig. 5*A*). In contrast, although there was not a significant difference between hydrocortisone and placebo [$t_{(24)} = -0.69$, $p = 0.50$, $d = -0.14$], there was no reliable subsequent memory effect for memories encoded under cortisol [mean difference = 0.38; SD = 4.75, $t_{(25)} = 0.41$, $p = 0.68$, $d = 0.081$]. Considering these effects within hippocampal subfields, we found a similar pattern in CA23DG (subsequent memory effect under placebo [$t_{(24)} = 2.26$, $p = 0.033$, $d = 0.45$], but not hydrocortisone [$t_{(24)} = 0.14$, $p = 0.89$, $d = 0.28$]; main effects and interactions [p values > 0.2]), but not CA1 (no subsequent memory effects under any conditions; Fig. 5*B*,*C*)]. This dissociation is consistent with prior work and the the proposed role of CA23DG in supporting distinct episodic memories (Eldridge et al., 2005; Carr et al., 2010). Together, these results converge with prior demonstrations that stress can alter univariate mechanisms of hippocampal memory formation (Henckens et al., 2009; Qin et al., 2012).

Discussion

Here, we combined behavior, high-resolution imaging of the human hippocampus, and pharmacological manipulation of hydrocortisone to provide novel insight into how hippocampal circuitry and representations scaffold associative memory enhancements under stress. First, we demonstrated behaviorally that cortisol enhances encoding of subjectively arousing associations. We then demonstrated a role for cortisol in enhancing functional interactions between hippocampal subfields; this intrahippocampal connectivity supported memory broadly under placebo, but prioritized emotional memory and tracked subjective arousal under cortisol. Last, we demonstrated that cortisol can alter how memories are encoded into the hippocampus, shifting the relationship between neural similarity and memory from negative under placebo to positive under cortisol. Together, these data provide evidence that mechanisms within the hippocampus can support associative memory enhancements under stress.

Although cortisol administration before encoding did not impact memory overall, cortisol enhanced associative memory for participants who experienced greater subjective arousal (across both the Emotional and Neutral blocks). This arousal-specific enhancement of memories under stress has been demonstrated previously and highlights the importance of assessing subjective arousal when measuring stress effects on memory (Buchanan and Lovallo, 2001; Abercrombie et al., 2003, 2006; Goldfarb et al., 2019), rather than focusing on broadly arousing versus nonarousing stimulus categories. However, most prior work focused on negative affect (Abercrombie et al.,

2003, 2006; Goldfarb et al., 2019). By using emotional stimuli (alcoholic beverages) that could be perceived as positive or negative, we demonstrated that cortisol can enhance memory for emotionally arousing, positive associations. This finding adds to burgeoning literature that acute stress promotes positive emotional memories (Kamp et al., 2019), and accords with work outside the stress domain demonstrating that positive emotion can bolster associative memory (Madan et al., 2019). Relatedly, cortisol amplified the perceived emotional salience of memoranda, with participants less likely to rate associations as "neutral" (similar to Abercrombie et al., 2003). Importantly, this cortisol-induced shift in affect valuation was specific to the encoded associations, and did not reflect a broader hydrocortisone-induced change in affect.

By combining behavior and neuroimaging, we identified hippocampal mechanisms underlying these cortisol-associated memory enhancements. High-resolution fMRI enabled us to evaluate hippocampal subfields, inspired by rodent findings of divergent stress effects across subfields (e.g., Alkadhi, 2019) and human structural imaging delineating subfield-specific effects of chronic stress and post-traumatic stress disorder (Wang et al., 2010; Nolan et al., 2020; Weis et al., 2021). This approach enabled precise localization of hippocampal contributions (rather than aggregating across the whole hippocampus) (e.g., van Stegeren, 2009; Lovallo et al., 2010; Qin et al., 2012) and revealed a novel role for glucocorticoids in enhancing human hippocampal function: connectivity among hippocampal subfields was enhanced under hydrocortisone. Prior rodent work similarly suggests that stress may alter (Jacinto et al., 2013) or enhance (Stepan et al., 2012) memory-related theta oscillations within the hippocampus. Importantly, this enhancement was specific to the hippocampal circuit; amygdala-hippocampal connectivity was not altered by hydrocortisone. Although this may be surprising given prior demonstrations of stress-induced enhancements of hippocampal–amygdala connectivity (Ghosh et al., 2013; Vaisvaser et al., 2013), the full stress response includes processes beyond cortisol (e.g., adrenergic effects on the amygdala can modulate hippocampal cortisol effects) (see Joëls and Baram, 2009). Cortisol alone can even reduce hippocampal–amygdala coupling (Henckens et al., 2012).

In addition to a broad enhancement with hydrocortisone, intrahippocampal connectivity differentially related to associative memory under cortisol and placebo. Under placebo, intrahippocampal (CA1-CA23DG) connectivity positively predicted memory, consistent with theorized roles for this circuit (Schapiro et al., 2017). Under cortisol, however, higher connectivity tracked better emotional, but not neutral memory. This finding suggests that the "typical" intrahippocampal mechanism supporting memory encoding may be repurposed under cortisol to prioritize emotional memory. Highlighting the importance of the emotional nature of these associations, connectivity under cortisol also tracked subjective arousal and valence. Interestingly, these affective hippocampal dynamics were specific to associations from the Emotional block, despite behavioral evidence that subjective arousal broadly tracks memory across blocks. Thus, future work is needed to understand the separable contributions of general, category-level emotional arousal (i.e., whether an association contains a putatively emotional vs neutral stimulus) and participant-specific arousal responses on explaining the relationship between hippocampal connectivity and memory.

The connectivity results indicate a common mechanism supporting associative memory: intrahippocampal connectivity broadly promotes memory under placebo but selectively promotes emotional memory under cortisol. In contrast, the pattern similarity findings indicate diverging hippocampal encoding processes. Under placebo, pattern dissimilarity predicted better subsequent memory. This is consistent with prior empirical work (LaRocque et al., 2013; Favila et al., 2016; Chanales et al., 2017; Wanjia et al., 2021) and theoretical models of hippocampal function, which posit that distinct neural representations (particularly in CA2/3/DG) support episodic memory (McClelland et al., 1995; Brunec et al., 2020). In contrast, under cortisol, pattern similarity positively predicted memory. Closer examination of our data suggests an affect-driven mechanism. First, although the similarity–memory association did not interact with block, greater similarity broadly tracked emotional memory (regardless of pill). Second, we observed overall greater similarity for emotional compared with neutral stimuli (again, regardless of pill). This pattern was not observed in LOC, suggesting that it was not driven by perceptual features. These results may converge with findings that pattern similarity at encoding (across many brain regions) predicts emotional memory (Visser et al., 2013; Tambini et al., 2017). Thus, one interpretation of the similarity–memory relationships for neutral memoranda (negative under placebo but positive under hydrocortisone) is that, with hydrocortisone, emotional encoding mechanisms are engaged to support memory.

Considered together, the connectivity and pattern similarity analyses provide evidence that the hippocampus can support enhanced memory formation under hydrocortisone. These two signals may serve distinct encoding purposes: intrahippocampal connectivity primarily explained memory for emotional associations, and CA23DG similarity primarily accounted for memory for neutral information. Despite this robust evidence for hippocampal contributions to enhanced memory under hydrocortisone, we found preliminary evidence for a blunted univariate hippocampal subsequent memory effect. We interpret these results with caution, given that the difference between placebo and hydrocortisone was not significant. We speculate that this reduced effect may be a consequence of our direct glucocorticoid manipulation, which differs from prior work using acute stressors that evoke both glucocorticoid and adrenergic mechanisms (Henckens et al., 2009; Qin et al., 2012). Nevertheless, the directionality of this effect is consistent with past reports (Qin et al., 2012), which have been interpreted as evidence against hippocampal involvement in stress-induced memory enhancements. Despite replicating this canonical "negative hippocampal" result, our findings challenge this interpretation by providing evidence that intrahippocampal dynamics under cortisol can indeed predict subsequent memory.

We note several limitations to these findings. First, although we used a controlled pharmacological manipulation to isolate effects of glucocorticoids, the stress response is multifaceted, involving myriad neurochemical systems operating over distinct timescales and brain networks (Hermans et al., 2014; Schwabe et al., 2022). By selectively manipulating cortisol, our findings cannot reveal the full effects of acute stress on encoding (perhaps explaining some surprising results, such as the lack of amygdala involvement). Future work systematically manipulating multiple stress hormones (e.g., van Stegeren et al., 2010) or assaying multiple components of the stress response under acute stress will be critical for elucidating which mechanisms presented here generalize to other facets of stress reactivity. Second, although the 24 h delay between encoding and retrieval allows us to exclude possible hydrocortisone effects on retrieval processes, exposure to hydrocortisone before encoding can potentially modulate both encoding and consolidation. As peripheral cortisol and intrahippocampal connectivity were both elevated throughout encoding,

it does appear that our manipulation impacted the encoding process. However, glucocorticoids can also exert slower, genomic effects (Schwabe et al., 2022), which modulate postencoding consolidation processes. Comparing the current findings to hydrocortisone administration immediately after encoding would help resolve this mechanism. Last, we observed worse memory for emotional compared with neutral associations, even after hydrocortisone. This differs from prior work demonstrating emotional memory enhancements under stress and cortisol (Buchanan and Lovallo, 2001; Kuhlmann and Wolf, 2006), including for positive stimuli (Kamp et al., 2019). One possibility is that the emotional stimuli (alcoholic beverages) were more conceptually similar to one another than the neutral stimuli, creating more interference in memory. Nevertheless, we note that individual differences in physiological (S. Segal et al., 2014) and subjective arousal (Goldfarb et al., 2019) have previously been identified as key modulators of stress and cortisol effects on memory, consistent with our observed relationship between subjective arousal and memory under cortisol.

In conclusion, we used a within-participant pharmacological manipulation to reveal the specific role of cortisol in altering hippocampal memory encoding. In doing so, we reveal novel avenues for hydrocortisone to enhance hippocampal function to promote later memory, pushing against models that stress impairs hippocampal function and thus requires other neural substrates to support memory (Kim and Diamond, 2002; Schwabe et al., 2022). By uncovering positive cortisol effects on hippocampal function, our results highlight the importance of considering multiple encoding mechanisms when assessing the effects of cortisol and stress on memory; whereas cortisol may impair some hippocampal encoding mechanisms, it may enhance or alter other avenues by which the hippocampus drives successful memory.

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