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Pattern separation and source memory engage distinct hippocampal and neocortical regions during retrieval

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Title: Pattern separation and source memory engage distinct hippocampal and neocortical regions during retrieval

Abbreviated title:

Pattern separation and source memory at retrieval

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1 **Abstract**

2 Detailed representations of past events rely on the ability to form associations between items
3 and their contextual features (i.e. source memory), as well as the ability to distinctly represent a
4 new event from a similar one stored in memory (i.e. pattern separation). These processes are
5 both known to engage the hippocampus, though whether they share similar mechanisms
6 remains unclear. It is also unknown if, and in which region(s), activity related to these processes
7 overlaps and/or interacts. Here, we used high-resolution fMRI to examine the contributions of
8 hippocampal subfields and neocortical areas to pattern separation and source memory with an
9 experimental paradigm that concurrently tested both. During encoding, male and female human
10 subjects incidentally studied items in one of four quadrants on the screen. During test, they
11 viewed repeated items (targets), similar items (lures), and new items (foils) and were asked to
12 indicate whether each item was old, similar, or new. Following each item judgment, subjects
13 were asked to indicate the quadrant in which the original stimulus was presented. Thus, each
14 lure trial had a lure discrimination component (taxing pattern separation) and a location
15 judgment (source memory). We found two main response profiles: 1) pattern separation-related
16 signals in DG/CA3 and perirhinal cortex and 2) source memory signals in posterior CA1,
17 parahippocampal cortex, and angular gyrus. Whole-brain voxelwise analysis revealed that
18 activity related to lure discrimination and source memory was largely non-overlapping. These
19 findings suggest that distinct processes underlie the retrieval of pattern separated item
20 representations and recollection of source information.

21

22 **Significance Statement**

23 Recalling past events with detail and accuracy depends on the ability to remember the
24 contextual features of an event (i.e. source memory) as well as the ability to distinguish among
25 similar events in memory (i.e. pattern separation). Previous work has shown that these
26 processes are behaviorally dissociable (e.g. people can have clear memory for context but

27 misidentify people or items). However, both processes engage the hippocampus, and it is
28 unclear whether they rely on shared or distinct neural mechanisms. Here, we used high-
29 resolution fMRI to concurrently assess hippocampal and neocortical activity related to source
30 memory and pattern separation. We found that activity related to these processes was largely
31 nonoverlapping, shedding light on two complementary but distinct mechanisms supporting
32 episodic memory.

33 Introduction

34 Detailed episodic memories depend on the ability to form associations between items and
35 contexts (i.e. source memory), as well as the ability to distinguish among similar items or events
36 in memory (i.e. pattern separation). A wealth of evidence indicates that source memory relies on
37 the hippocampus, which is thought to represent the association between items and context
38 (Diana, Yonelinas, and Ranganath 2007). Studies in rodents have shown that hippocampal CA1
39 “place cells” can code for associations between objects and locations (Komorowski, Manns, and
40 Eichenbaum 2009) while studies in humans using high-resolution fMRI have shown increased
41 activity in the CA1 and subiculum during associative memory encoding and retrieval (Viskontas
42 et al. 2009; Suthana et al. 2015; Eldridge 2005). Studies of source memory typically compare
43 activity related to item recognition with (S+) and without (S-) a specific contextual detail (e.g.
44 spatial location) and tend to equate item recognition alone (S-) with less detailed, lower fidelity
45 memory (Hutchinson et al. 2014; Frithsen and Miller 2014). These studies often fail to show
46 hippocampal engagement for item recognition without retrieval of associated context (S-).
47 However, item memory itself can be highly detailed. Distinct, high fidelity representations of
48 items must be formed (via pattern separation) in order to discriminate them from similar items in
49 memory. Like source memory, pattern separation is thought to rely on the hippocampus, with
50 evidence in rodents (Leutgeb et al. 2007; Neunuebel and Knierim 2014) as well as in human
51 mnemonic discrimination paradigms (Bakker et al. 2008; Berron et al. 2017) suggesting that the
52 dentate gyrus (DG) plays a critical role in orthogonalizing overlapping inputs.

53

54 Outside the hippocampus, a broad network of posterior-medial cortical areas are thought to
55 support context and source memory (Ranganath and Ritchey 2012; Reagh and Ranganath
56 2018). The parahippocampal cortex (PHC) encodes spatial/contextual information alongside the
57 hippocampus, while activity in the lateral posterior parietal cortex, particularly the angular gyrus,
58 is associated with retrieval of episodic detail (Johnson, Suzuki, and Rugg 2013; Hutchinson et

59 al. 2014). More recently, studies have found that cortical regions outside of the hippocampus
60 might also contribute to pattern separation (Reagh and Yassa 2014; Leal and Yassa 2018). For
61 example, recent work from our group showed that the perirhinal cortex (PRC), part of the ventral
62 “what” stream projecting to the hippocampus, is engaged during mnemonic discrimination of
63 similar objects (Reagh and Yassa 2014).

64

65 Using a well-validated item discrimination task that was modified to include a source memory
66 component, previous work in our lab has shown that correct source memory judgements can
67 occur in the absence of pattern separation (i.e. false alarms), indicating that these processes –
68 which both presumably hinge on detailed hippocampal representations – are at least
69 behaviorally dissociable (Kim and Yassa 2013). However, the extent to which these processes
70 produce distinct or overlapping signals in hippocampal subregions and cortical areas is
71 unknown. The present study used high-resolution fMRI (1.8 mm with near whole brain
72 coverage) to simultaneously assess hippocampal subfield and cortical activity during
73 discrimination of similar lure items and source memory judgments for these items. Prior fMRI
74 studies have observed activity in the DG/CA3 region during correct rejection of similar lures to
75 be on par with that of novel foils (Bakker et al. 2008). This pattern of activity is consistent with a
76 pattern separation signal in that similar items are treated like new items, and do not induce the
77 repetition suppression (i.e. fMRI adaptation) observed for identical repetitions. We predicted that
78 we would see this pattern separation signal in the DG/CA3 during correct rejection of similar lure
79 items, while other subregions of the hippocampus (CA1 and subiculum) would be sensitive to
80 source memory (higher levels of activity for correct source vs. incorrect source judgments).
81 Since we acquired near whole brain fMRI coverage, we were also able to examine what regions
82 outside of the hippocampus displayed dissociated or overlapping pattern separation and source
83 memory signals.

84

85 **Materials and Methods**

86 **Subjects**

87 Thirty-one healthy subjects were initially recruited for the study from the University of California,
88 Irvine and the greater Orange County community. Of this initial sample, one was excluded due
89 to equipment malfunction at the scanner, one was excluded due to premature withdrawal from
90 the experiment, two were excluded due to chance-level performance on at least one task
91 condition, and two were excluded due to excessive motion during scanning. This yielded a final
92 sample of 25 subjects included in our analyses (17 female, age range = 18-29 years, mean =
93 20.6 years, SD = 2.47 years). All subjects were screened for neurological conditions (e.g.,
94 history of stroke or mental illness), sleep deprivation, and major symptoms of depression (via
95 the Beck Depression Inventory) at recruitment. Subjects gave written informed consent in
96 accordance with the UC Irvine Institutional Review Board and were compensated for their
97 participation.

98

99 **Task**

100 The task was adapted from our prior work (Kim and Yassa 2013), and optimized for use in the
101 MRI scanner (Fig. 1A). Participants first completed an incidental study phase in which 226
102 common objects appeared in one of four positions on the screen for 3 seconds (1 second inter-
103 stimulus interval), and were tasked with indicating whether each object would be more
104 commonly found indoors or outdoors. The screen was divided into four equal quadrants, and
105 objects appeared in one of the four positions (randomized across the stimulus set for each
106 subject). Following the study phase, a surprise test phase was conducted consisting of 300
107 trials. Of the 300, 74 objects were completely novel (foils), 74 were identical to studied objects
108 (targets), and 150 were similar but not identical to studied objects (lures). Like the study phase,
109 objects appeared on the screen for 3 seconds, and subjects were tasked with judging whether
110 each object was “old,” “similar,” or “new” (corresponding to targets, lures, and foils respectively).

111 Additionally, following the item judgment, participants completed a source memory judgment. If
112 participants selected “old” or “similar,” following a 1 second delay, they were prompted with a
113 screen showing numbered quadrants and were given 3 seconds to select the quadrant where
114 they had seen the original object. In the case of lures, it was made clear to the subjects that the
115 source judgment is of the studied item to which the lure is similar (yielding a condition in which
116 pattern separation has presumably taken place, as well as contextual memory retrieval). If
117 participants selected “new,” instead of a quadrant judgment, they were prompted to indicate
118 whether they were “sure” or “unsure” about their judgment (we did not differentiate between
119 these particular judgments in our analyses, and only included this follow-up for foils to match the
120 time taken by source judgments in target and lure trials). Responses were made via button-
121 press, and on-screen icons corresponding to each button illuminated in red when pushed to
122 assist in mapping participants onto their desired responses.

123

124 **MRI Acquisition**

125 Neuroimaging data were acquired on a 3.0 Tesla Philips Achieva scanner, using a 32-channel
126 sensitivity encoding (SENSE) coil at the Neuroscience Imaging Center at the University of
127 California, Irvine. A high-resolution 3D magnetization-prepared rapid gradient echo (MP-RAGE)
128 structural scan (0.75mm isotropic voxels) was acquired at the beginning of each session:
129 repetition time (TR) = 11ms, echo time (TE) = 4.43ms, 200 slices, 0.75mm isotropic, field of
130 view (FOV) = 231x240x150. Functional MRI scans consisted of a T2*-weighted echo planar
131 imaging (EPI) sequence using blood-oxygenation-level-dependent (BOLD) contrast: TR =
132 3000ms, TE = 26ms, flip angle = 70 degrees, 43 slices, 1.8 x 1.8mm in plane resolution, 1.8mm
133 slice stem thickness with a 0.2 mm gap, FOV = 180x77.4x180. Slices were acquired as a partial
134 axial volume and without offset or angulation, yielding near whole brain coverage. Four initial
135 “dummy scans” were acquired to ensure T1 signal stabilization. A total of 6 functional runs were

136 acquired for each participant, 2 study phases and 4 test phases. Each study run lasted 387
137 seconds (123 dynamics), and each test run lasted 468 seconds (150 dynamics).

138

139 **MRI Preprocessing and ROI Segmentation**

140 All neuroimaging data were preprocessed and analyzed using Analysis of Functional
141 NeuroImages (AFNI, version 17.2.00) (Cox 1996) on GNU/Linux and Mac OSX platforms.
142 Analyses largely took place in accordance with the standardized afni_proc.py pipeline. EPIs
143 were corrected for motion (3dvolreg) and slice timing (3dTshift), masked to exclude voxels
144 outside the brain (3dautomask), and were smoothed (3dmerge) using a 2.0mm Gaussian
145 FWHM kernel. Motion correction parameters were saved into text files for later use in linear
146 regression (see MRI Data Analysis below). Each run was also de-spiked to further reduce the
147 influence of motion on the data (3dDespike). Functional scans were aligned to each subject's
148 skull-stripped MP-RAGE (align_epi_anat.py). We used Advanced Normalization Tools (ANTs) to
149 warp each individual participant's structural scan into our custom in-house high-resolution
150 0.75mm isotropic template using SyN nonlinear registration (Avants et al. 2011). Parameters
151 from these warps were used to also warp functional scans into template space for group ROI
152 analyses. Masks were resampled to match the resolution of the smoothed fMRI data (2.0mm
153 isotropic) and were further masked to exclude partially sampled voxels within and across runs
154 (3dcalc). Finally, we normalized data to the global within-run mean (3dcalc) such that ensuing
155 beta coefficients reflect percent change from baseline.

156

157 We defined hippocampal ROIs based on our established protocols (e.g., Yassa et al. 2010;
158 Reagh and Yassa 2014) (Fig. 2). Briefly, segmentation of hippocampal subfields was conducted
159 in accordance with the SY protocol reported in Yushkevich and colleagues (Yushkevich et al.
160 2015) using our custom high-resolution group template, though the CA1-subiculum boundary
161 was updated to reflect recent efforts at harmonizing across hippocampal segmentation protocols

162 (Wisse et al. 2017). As with prior studies (Reagh, Murray, and Yassa 2017), we segmented
163 anterior versus posterior portions of hippocampal subfields given hypotheses about specific
164 posterior medial temporal lobe involvement in contextual memory (Ranganath and Ritchey
165 2012). This division was placed at the slice immediately posterior to the uncus apex, such that
166 our “anterior” hippocampal division refers specifically to the hippocampal head, whereas the
167 “posterior” division refers to the body and tail. The angular gyrus ROI was defined as an
168 inclusive ROI centered on the angular gyrus but including neighboring regions of the
169 posterior parietal cortex.

170

171 **Experimental Design and Statistical Analysis**

172 **Behavioral Analyses**

173 Statistical analyses were performed using GraphPad Prism 8.1.2. Trials were classified
174 according to item (old, similar, new) and source judgment (source correct and source incorrect),
175 and the proportion of responses for each trial type was calculated. To test for behavioral effects,
176 we ran a repeated measures ANOVA for both targets and lures with item response (old and
177 similar) and source memory (source correct and source incorrect) as within-subject factors.
178 Post-hoc t-tests were performed using Holm-Sidak’s multiple comparison test in order to
179 examine significant interactions.

180

181 **MRI Methods**

182 Only retrieval data were included in the analyses. We constructed a general linear model (GLM)
183 with regressors for target hits, lure correct rejections, and lure false alarms with both correct and
184 incorrect corresponding source judgments, as well as foil correct rejections (collapsing across
185 confidence judgments). Foil false alarms, target misses, lure misses, and non-response trials
186 were collapsed into a regressor of non-interest given their rarity and difficulties with regards to
187 interpretation. We additionally included regressors for six motion vectors derived from the

188 motion correction preprocessing step (x, y, z, pitch, roll, yaw). The GLM was run in AFNI using
189 3dDeconvolve. Deconvolution of the hemodynamic response was done using tent functions
190 covering stimulus onset to 15 seconds after onset with 6 estimator functions distributed across
191 this time window. Motion parameters were entered in to the model as explicit regressors to
192 reduce the influence of head movement on task-related parameter estimates, and non-response
193 trials were entered to exclude these ambiguous trials from affecting the model residuals.
194 Additionally, vectors modeling temporal drift were entered as regressors covering first, second,
195 and third-order polynomials. In generating our response estimates for our conditions of interest,
196 we explicitly subtracted novel foil rejections as a baseline condition. Briefly, this yields the
197 interpretation that deviations from baseline are likely memory-driven. For all functional runs, TRs
198 with motion exceeding 0.5mm frame displacement (but below our exclusion threshold of 3mm)
199 were censored from analyses, as well as the immediately preceding and following TRs. Finally,
200 global signal from the ventricles and white matter was excluded from gray matter voxels using
201 ANATICOR (Jo et al. 2010). These “data scrubbing” procedures were employed to exclude the
202 effects of head motion on activation profiles to the extent possible (Power et al. 2012).
203 Final beta weights entered in to second-level analyses consisted of the average of the first three
204 estimator functions (targeted to capture the peak of the BOLD response).

205

206 **ROI analyses**

207 For our region of interest (ROI) analyses, beta weights were converted to percent change from
208 baseline then extracted from a priori ROIs (3dmaskave). Statistical analyses were performed
209 using GraphPad Prism 8.1.2 and IBM SPSS 26.0. Repeated measures 2-way ANOVAs with lure
210 discrimination (lure correct rejection and lure false alarm) and source memory (correct and
211 incorrect) as within-subject factors were used to probe effects in hippocampal and neocortical
212 ROIs. In order to directly compare observed hippocampal pattern separation and source
213 memory effects, we converted the square root of partial eta squared for both the lure

214 discrimination and source memory effects to Fisher's z' . We then Z scored the difference in
215 these values across subregions (e.g. Z score of Fisher's z' (lure) in DG/CA3 - Fisher's z' (lure) in
216 CA1). Holm-Sidak correction across hippocampal subfields ($n = 12$) was used to examine which
217 hippocampal effects survived multiple comparison correction. For regions where we observed a
218 main effect of lure discrimination, we ran one-sample t-tests comparing activity for lure correct
219 rejections with baseline (foil correct rejections). In regions where activity was not consistent with
220 predicted pattern separation or source memory signals, target hits were included in the analysis.
221 For these regions, repeated measures 2-way ANOVAs were performed with item memory (lure
222 correct rejection, lure false alarm, and target hits) and source memory (correct and incorrect) as
223 within-subject factors. Post-hoc t-tests using Holm-Sidak's multiple comparison test were used
224 to test main effects of item memory.

225

226 **Voxel-wise analyses**

227 In addition to our hypothesis-driven ROI-based approach, we examined near-whole brain
228 exploratory functional maps of lure discrimination and source-related main effects, as well as
229 areas of overlap using AFNI, version 17.2.00. To do this, we entered each subject's beta
230 coefficients into a repeated measures ANOVA (3dANOVA3), with lure discrimination (lure
231 correct rejection and lure false alarm) and source memory (correct and incorrect) as within-
232 subject fixed factors, and subjects as a random factor. Significant activation maps were adjusted
233 for multiple comparisons using familywise error rate (FWE) correction, with minimum extent of
234 46 contiguous voxels at a threshold of $p < 0.05$ (3dClustSim, recently updated to address
235 unintended alpha inflation). For visualization, we binarized significant F-statistic maps for
236 individual effects of lure discrimination and source memory, and then combined them into a
237 single map using a simple step function (i.e., lure discrimination effect voxels received a value of
238 1, source effect voxels received a value of 2, and voxels featuring overlapping effects received a
239 combined value of 3).

240

241 **Results**

242 **Behavioral Findings**

243 We first examined the average proportion of old, similar, and new responses for each stimulus
244 type (target, lure, or foil) (Fig. 1B). Overall, subjects were able to correctly identify targets as old
245 (65%) and foils as new (69%), whereas lure items were often incorrectly identified as old (36%)
246 instead of similar (49%). This pattern of behavior indicates a distribution of lure correct
247 rejections and false alarms, and replicates previous results using the same task (Kim and Yassa
248 2013). Next, we examined performance on the second stage source memory judgement. We
249 ran a repeated measures ANOVA across item response (old and similar) and source memory
250 (source correct and source incorrect) for both targets and lures. For targets, we found a main
251 effect of item response and source memory, as well as an interaction (item response: $F(1, 24) =$
252 $53.4, p = 1.5 \times 10^{-7}$, source: $F(1, 24) = 5.7, p = 0.3$, interaction: $F(1, 24) = 16.6, p = 0.0004$), with
253 more target hits (targets correctly identified as old) than there were targets misidentified as
254 similar and more correct than incorrect source judgments. Post hoc t-tests showed that subjects
255 made correct source memory judgements more often for targets hits ($F(1, 24) = 5.7, p = 0.02$;
256 source correct vs. source incorrect: mean difference = 0.14, $p < 0.05$), indicating that when
257 subjects had a more accurate representation of the target item, they tended to have better
258 source memory for that item. For lures, we found there was a higher rate of correct rejections
259 (lures correctly identified as similar, LCR) than false alarms (lures misidentified as old, LFA)
260 ($F(1, 24) = 4.8, p = 0.04$) (Fig. 1C), but no significant difference in the number of correct and
261 incorrect source judgements ($F(1, 24) = 3.14, p = 0.09$). Critically, these data replicate previous
262 results indicating a behavioral dissociation between source memory and pattern separation,
263 showing that correct source memory judgments can occur in the absence of pattern separation
264 (i.e. false alarms) and that item-level pattern separation can occur with incorrect source memory
265 judgments.

266

267 Neuroimaging Findings

268 We used high-resolution fMRI (1.8 mm isotropic), allowing for near-whole brain acquisition, to
269 examine regional activity engaged during item and source memory judgements. For each ROI,
270 we ran a repeated measures ANOVA on lure items with lure discrimination (lure correct
271 rejection and lure false alarm) and source memory (source correct and source incorrect) as
272 fixed factors. For regions where we observed a main effect of lure discrimination, we ran t-tests
273 comparing activity for lure correct rejections with baseline (foil correct rejections). Figures 3-4
274 presents the percent change in signal for each region across all conditions of interest (lure
275 correct rejections, lure false alarms, and target hits, considered separately for Source+ and
276 Source- conditions).

277

278 Distinct hippocampal pattern separation and source memory signals

279 Activity in the left anterior DG/CA3 and bilateral posterior DG/CA3 was greater for correct
280 rejections than false alarms, with activity for correct rejections on par with that of foil correct
281 rejections (i.e. baseline) (Fig. 3C, E-F, left anterior DG/CA3: $F(1, 24) = 6.9$, $p = 0.016$, t-test
282 LCR vs. baseline: $t(24) = 0.46$, $p = 0.65$; left posterior DG/CA3: $F(1, 24) = 5.426$, $p = 0.029$, t-
283 test LCR vs. baseline: $t(24) = 1.3$, $p = 0.22$; right posterior DG/CA3: $F(1, 24) = 10.6$, $p = 0.003$, t-
284 test LCR vs. baseline: $t(24) = 0.35$, $p = 0.73$). This pattern of activity is consistent with a pattern
285 separation signal (Fig. 3A) in that correctly rejected lures are treated as if they were novel items
286 (i.e. foil correct rejections) while lures mistakenly identified as old show repetition suppression.
287 Activity in the right posterior CA1 was more robustly engaged for correct source judgments than
288 for incorrect source judgments (Fig. 3J, right posterior CA1: $F(1, 24) = 12.6$, $p = 0.002$),
289 consistent with a source memory signal (Fig. 3B). There was also a marginal effect of source in
290 the right posterior subiculum ($F(1, 24) = 2.7$, $p = 0.11$; Fig 3N). These source effects were also
291 observed when target hits were included in the analysis (right posterior CA1: $F(1, 24) = 18.8$, p

292 = 0.0002; right posterior subiculum: $F(1, 24) = 8.9, p = 0.006$). In order to more directly compare
293 pattern separation and source effects across subregions, we converted partial eta squared to
294 Fisher's z' , then Z scored the difference in these values across subregions. We found that the
295 pattern separation effect was marginally greater in the right posterior DG/CA3 (right posterior
296 DG/CA3 lure – right posterior CA1 lure Z difference = 1.8, $p = 0.07$); and that the source effect
297 was marginally greater in the right posterior CA1 (right posterior DG/CA3 source - right posterior
298 CA1 source Z difference = -1.9, $p = 0.05$). A similar pattern was found when comparing effects
299 in the left anterior and posterior DG/CA3 and CA1 (left anterior DG/CA3 lure - right posterior
300 CA1 lure Z difference = 1.4, $p = 0.16$; left anterior DG/CA3 source - right posterior CA1 source Z
301 difference = -2.05, $p = 0.04$; left posterior DG/CA3 lure - right posterior CA1 lure Z difference =
302 1.2, $p = 0.2$; left posterior DG/CA3 source - right posterior CA1 source Z difference = -1.85, $p =$
303 0.06). The pattern separation effect in the right posterior DG/CA3 as well as the source effect in
304 the right posterior CA1 survived Holm-Sidak correction for multiple comparisons across
305 hippocampal subfields ($n = 12$).

306

307 **Distinct neocortical pattern separation and source memory signals**

308 Activity in the right PRC was consistent with a pattern separation signal, with activity for correct
309 rejections greater than for false alarms and on par with that of foil correct rejections (Fig. 4A,
310 right PRC: $F(1, 24) = 5.8, p = 0.02$, t-test LCR vs. baseline $t(24) = -1.1, p = 0.29$). Activity in the
311 right PHC and bilateral angular gyrus was more robustly engaged for correct source judgments
312 than for incorrect source judgments, consistent with a source memory signal (Fig. 4B,C,F, right
313 PHC: $F(1, 24) = 7.4, p = 0.01$; left angular gyrus: $F(1, 24) = 11.06, p = 0.003$; right angular
314 gyrus: $F(1, 24) = 8.3, p = 0.008$). These source effects remained significant when target hits
315 were included in the analysis (right PHC: $F(1, 24) = 14.7, p = 0.001$; left angular gyrus: $F(1, 24)$
316 = 13.3, $p = 0.001$; right angular gyrus: $F(1, 24) = 9.8, p = 0.005$).

317

318 **Familiarity and novelty signals in left posterior CA1 and left PHC**

319 Activity in the left posterior CA1 and left PHC showed response profiles that were not consistent
320 with predicted pattern separation or source memory signals or an interaction between the two.
321 In the left posterior CA1 there was a main effect of source, however, activity for incorrect source
322 judgments was greater than for correct source judgments (S- > S+) ($F(1, 24) = 5.9, p = 0.02$). In
323 the left PHC there was a main effect of lure discrimination, with activity for lure correct rejections
324 greater than for lure false alarms ($F(1, 24) = 6.3, p = 0.02$). However, activity for lure correct
325 rejections was increased relative to baseline (LCR > baseline) ($t(24) = 2.5, p = 0.02$). As such,
326 target hits were included in the ANOVA to better examine the engagement of these regions
327 during recognition memory, resulting in a 2 x 2 repeated measures ANOVA with item memory
328 (lure correct rejections, lure false alarms, and target hits) and source memory (source correct
329 and source incorrect) as fixed factors. When target hits were included, we observed an effect of
330 item memory (Fig. 3I, $F(2, 48) = 5.4, p = 0.008$) and source ($F(2, 48) = 6.2, p = 0.02$) in the left
331 posterior CA1, with post-hoc tests showing greater activity for targets hits than for lure correct
332 rejections and lure false alarms (LCR vs. Hits: mean difference = -0.07, $p = 0.01$; LFA vs. Hits:
333 mean difference = -0.06, $p = 0.03$). This pattern of activity could reflect a “familiarity signal” that
334 is often observed in the hippocampus, with greater activity for previously seen items than for
335 novel items (Rutishauser et al. 2015; Reagh, Watabe, et al. 2014). The left PHC showed an
336 effect of both item (Fig. 4E, $F(2, 48) = 6.7, p = 0.003$) and source ($F(1, 24) = 7.9, p = 0.01$), with
337 greater activity for correct rejections (LCR vs. LFA: mean difference = 0.08, $p = 0.01$; LCR vs.
338 Hits: mean difference = 0.1, $p = 0.004$) and for incorrect source judgements. Although this
339 region showed greater activity for lure correct rejections than for lure false alarms, this does not
340 follow the standard pattern separation signal seen in many fMRI studies, since activity for lure
341 correct rejections was not on par with that of foil correct rejections (LCR > FCR). Rather, the
342 increased activity for lure correct rejections could reflect particularly robust item novelty

343 signaling. Uncertainty about the source of item information could contribute to the increased
344 activity for source incorrect trials observed in both the left posterior CA1 and left PHC.

345

346 **Voxelwise analysis**

347 To identify regions where there might be overlapping effects of both lure discrimination and
348 source memory that were outside of our *a priori* regions of interest, we conducted an exploratory
349 voxelwise analysis. We ran a repeated measures ANOVA with lure discrimination (lure correct
350 rejection vs. false alarm) and source memory (source correct vs. source incorrect) as fixed
351 factors. Figure 5 shows clusters of voxels that showed a main effect of lure discrimination (red)
352 or source (blue), as well as voxels that showed a main effect of both lure discrimination and
353 source (green). This analysis revealed three major themes. First, activity related to lure
354 discrimination drove robust activity in the ventral visual stream and the anterior MTL, notably the
355 anterior hippocampus and PRC. Conversely, activity related to source memory drove activity in
356 regions such as medial prefrontal cortex, retrosplenial cortex, and angular gyrus, which have
357 often been implicated in source memory (Hutchinson et al. 2014; Johnson, Suzuki, and Rugg
358 2013; Ranganath and Ritchey 2012). Additionally, source memory effects were largely present
359 in the posterior MTL, including the hippocampus and PHC. Second, though this was less
360 apparent in our ROI-based analyses, lure discrimination and source effects appeared to show a
361 surprising degree of laterality in the MTL. In addition to anterior-posterior dissociations, lure
362 related activity in the MTL was more left-lateralized, whereas source memory related activity
363 was more right-lateralized. Third, despite some shared voxels in retrosplenial cortex, precuneus,
364 and right angular gyrus, lure discrimination and source memory activity maps were surprisingly
365 nonoverlapping. This is particularly striking given the many lure or source driven voxels that are
366 adjacent but not shared.

367

368 **Discussion**

369 We describe a high-resolution fMRI study designed to concurrently test source memory and
370 pattern separation and to assess hippocampal subfield and neocortical contributions to these
371 processes. Replicating our previous behavioral work, we found that correct source memory
372 judgments can occur in the absence of pattern separation (and vice versa), indicating that these
373 processes are behaviorally dissociable. We also found a dissociation in the signal profiles
374 associated with these processes, with hippocampal subfields and cortical ROIs showing largely
375 nonoverlapping effects. No interaction between source memory and lure discrimination was
376 observed in any of the regions tested. These findings suggest that although source memory and
377 pattern separation both contribute to detailed episodic memory, and both depend on the
378 hippocampus, these processes are supported by distinct neural mechanisms.

379

380 As predicted, we observed a signal in the DG/CA3 consistent with pattern separation, with
381 activity for lure correct rejections greater than for lure false alarms and on par with activity for
382 novel foils. This is consistent with this region's proposed role in orthogonalizing overlapping
383 input. We observed a source memory signal in the right posterior CA1 and right posterior
384 subiculum, in line with previous studies showing increased activity at retrieval for correct
385 associative memory judgments in these regions (Eldridge 2005; Stevenson et al. 2018;
386 Viskontas et al. 2009). No hippocampal subfield showed overlapping effects of lure
387 discrimination and source memory or a significant interaction.

388

389 We note that our method of testing mnemonic discrimination and an accompanying lack of
390 BOLD response adaptation in response to similar items is an indirect measure of pattern
391 separation. Additionally, despite the observed dissociation in signal profiles across hippocampal
392 subfields, these data should not be taken to suggest that these regions are not involved in both
393 source memory and pattern separation processes. There is much evidence to suggest that the
394 DG/CA3 region supports source memory when there is overlap between items and their

395 associated context (e.g. parking a car in the same lot every day). Additionally, the CA3
396 subregion has long been thought to be involved in pattern completion, or the retrieval of
397 associated information when presented with a partial cue (O'Reilly and Norman 2002; Kumaran,
398 Hassabis, and McClelland 2016). This process is thought to be critical to source memory (e.g.
399 viewing an item might trigger retrieval of the location of that item). The CA1 is thought to support
400 pattern separation by linking pattern separated representations in the CA3 back to input
401 patterns in the entorhinal cortex (EC) (Norman 2010). The CA1 might also contribute to
402 mnemonic discrimination by acting as a “match-mismatch” detector, signaling discrepancies
403 between the retrieved original item and the lure (Duncan et al. 2012). As the subiculum serves
404 as the main output of the hippocampus, this region is likely to be involved in many hippocampal-
405 dependent processes, including source memory and pattern separation. Accordingly, we
406 maintain that both source memory and pattern separation rely on complex hippocampal circuits
407 rather than distinct regions. Indeed, a recent study by Libby and colleagues (Libby et al. 2018)
408 found that patterns of hippocampal activity discriminated among similar items and similar
409 contexts, but generalized across similar items-in-context, suggesting complex interactions.
410 However, the dissociated signals elicited by source memory and pattern separation in the
411 present study indicate that these processes may rely on distinct neural mechanisms that can be
412 identified when the two processes are pitted against each other in an experimental design.

413

414 This dissociation was also observed outside of the hippocampus, with the PHC and angular
415 gyrus showing increased activity for correct source judgments (no pattern separation signal) and
416 the PRC showing a pattern separation signal (no source memory signal). This pattern of activity
417 is consistent with the well-established role of the PHC in spatial/contextual processing and the
418 role of the angular gyrus in the retrieval of episodic details. As part of the ventral “what” stream,
419 the PRC has long been known to be involved in item recognition. Recent work from our group
420 using a similar task has shown that this region is engaged during mnemonic discrimination of

421 similar objects (Reagh and Yassa 2014). The current results replicate this effect, adding to a
422 growing literature examining pattern separation-like effects in cortical areas (Pidgeon and
423 Morcom 2016; Reagh and Yassa 2014; Kent et al. 2016). The PRC is thought to be involved in
424 complex perceptual discriminations, which may contribute to subsequent mnemonic
425 discrimination (Barense, Henson, and Graham 2011). These results are also consistent with the
426 representational-hierarchical model which holds that the PRC represents complex item features
427 that are less likely to be shared among similar items and, as such, can resolve interference
428 among these items (Kent et al. 2016). Though this may not reflect pattern separation in the
429 traditional sense of computational models, it does amount to a manner of discriminating among
430 overlapping inputs. The dissociation between source memory and pattern separation signals
431 was further corroborated by a voxelwise analysis which revealed that, except for some shared
432 voxels in posterior cortical areas, activity related to lure discrimination and source memory was
433 largely non-overlapping.

434

435 While we attempted to interpret the results within the framework of our hypotheses, we cannot
436 rule out the possibility that other factors might have contributed to the observed pattern of
437 results. Since our experimental paradigm used similar objects to tax pattern separation and
438 spatial location to test source memory, one alternative interpretation is that the observed pattern
439 separation and source memory effects could reflect object versus spatial processing,
440 respectively. However, this interpretation does not explain why the observed effects fit the
441 specific response profile delineated by our predicted pattern separation signal, with activity for
442 correct rejections greater than for false alarms and on par with that of foil correct rejections. In
443 addition, if this effect is being driven solely by object processing, not pattern separation, we
444 wouldn't necessarily expect to see this effect in the DG/CA3, since object recognition often does
445 not engage the hippocampus. In contrast, object recognition in the face of interference –
446 putatively pattern separation – does engage the DG/CA3, suggesting that this is what is driving

447 the observed effects in this region. The dissociation observed in the PRC and PHC is consistent
448 with the object versus spatial interpretation, as these regions are known to be involved in object
449 and spatial processing, respectively. However, since the DG/CA3 has been shown to respond to
450 both object and spatial processing, domain specificity doesn't cleanly explain the observed
451 pattern of results. Future studies could utilize different types of pattern separation or source
452 judgments to determine if the observed phenomena are specific to object/spatial processing or
453 generalize across modalities.

454

455 A second possibility is that the pattern separation and source memory effects could have been
456 driven by encoding versus retrieval, respectively, since correct rejection of similar lures could
457 involve relatively more encoding-related processes. However, encoding and retrieval are highly
458 dynamic processes and a combination of encoding and retrieval processes contribute to both
459 item discrimination and source memory. For example, correct rejection of similar lures likely
460 involves a "recall-to-reject" strategy. A third possibility is that the pattern separation and source
461 memory effects could have been driven by pattern separation and pattern completion,
462 respectively, since source memory judgments involve retrieving a spatial location based on a
463 partial cue (the item). However, pattern separation and pattern completion are not mutually
464 exclusive and, much like encoding and retrieval-related processes, are likely involved in all of
465 our different trial types. For example, we could argue that item discrimination also involves
466 pattern completion since these trials likely involve a "recall-to-reject" strategy, as noted above.
467 As such, neither encoding versus retrieval nor pattern separation versus pattern completion
468 dissociations clearly explain the observed pattern of results.

469

470 Source memory effects were largely present in the posterior MTL, including the posterior
471 hippocampus and PHC, consistent with recent theories including this region as part of a highly
472 interconnected posterior network thought to be involved in contextual and spatial processing,

473 including the angular gyrus and retrosplenial cortex (Ranganath and Ritchey 2012).
474 Interestingly, pattern separation effects were present in both the anterior and posterior DG/CA3.
475 While some theories have linked the anterior hippocampus with more coarse, gist-based
476 memory, as noted in Poppenk et al. this might reflect the uneven distribution of the DG/CA3
477 subfield across the long axis of the hippocampus, with the posterior hippocampus having a
478 higher ratio of DG/CA3 compared with other subfields (Poppenk et al. 2013). Our results
479 suggest that, at least within the DG/CA3, both the anterior and posterior hippocampus supports
480 detailed episodic memory.

481

482 These results highlight the value of testing multiple aspects of episodic memory in a single
483 experimental paradigm. Though source memory and pattern separation both engage the
484 hippocampus, by concurrently testing both processes we were able to observe if, and where,
485 activity related to these processes overlaps and/or interacts. Here, we found that source
486 memory and pattern separation seem to utilize distinct mechanisms. This dissociation may
487 explain why people can have very clear memory for context but misidentify specific people or
488 items. Future studies can examine the circumstances under which source memory and pattern
489 separation might interact.

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629 **Figure Captions**

630 **Figure 1. Task schematic and performance.** (A) During incidental encoding, subjects viewed
631 items in one of four quadrants on the screen. During test, they viewed some of the same items
632 (targets), some similar items (lures), and some new items (foils) and were asked to indicate
633 whether each item was old, similar, or new. Following the item judgement, if subjects selected
634 “old” or “similar” they were asked to select the quadrant where they had seen the original object.
635 If participants selected “new,” instead of a quadrant judgment, they were prompted to indicate
636 whether they were “sure” or “unsure” about their judgment. (B) Proportion of ‘old’, ‘similar’, and
637 ‘new’ responses for each stimulus type. (C) Proportion of source correct (S+) and source
638 incorrect (S-) responses for lures called ‘old’ (lure false alarms (LFA)) or ‘similar’ (lure correct
639 rejections (LCR)). Error bars indicate s.e.m.

640

641 **Figure 2.** Regions of interest. Regions of interest are displayed in representative slices moving
642 from anterior (top left) to posterior (bottom right). Corresponding slices without regions of
643 interest are also displayed. SUB: subiculum; PRC: perirhinal cortex; PHC: parahippocampal
644 cortex; AG: angular gyrus; Ant.: anterior; Post.: posterior.

645

646 **Figure 3.** Dissociated pattern separation and source memory signals in hippocampal subfields.
647 (A) Schematic of the predicted pattern separation signal (blue dots), where activity for lure
648 correct rejections is on par with foil correct rejections (FCR, baseline) and lure false alarms
649 show repetition suppression (LCR > LFA). (B) Schematic of the predicted source memory signal
650 (orange dots), where activity for correct source judgments is greater than for incorrect source
651 judgments. Activity in the left anterior DG/CA3 (C) and bilateral posterior DG/CA3 (E-F) was
652 greater for correct rejections, consistent with a pattern separation signal. Activity in the right
653 posterior CA1 (J) was greater for correct source memory judgments, consistent with a source
654 memory signal. (N) Marginal effect of source in the right posterior SUB ($p = 0.065$). Activity in

655 the left posterior CA1 (I) showed a response profile that was not consistent with predicted
656 pattern separation or source memory signals. When target hits were included in the analysis,
657 there was an effect of item memory and source in this region, with greater activity for target hits
658 than for LCR and LFA. The dotted rectangle indicates conditions that were included in the 2-way
659 ANOVA. Activity in all other hippocampal ROIs are also presented. Foil correct rejections were
660 used as baseline. Error bars indicate s.e.m. SUB: subiculum.

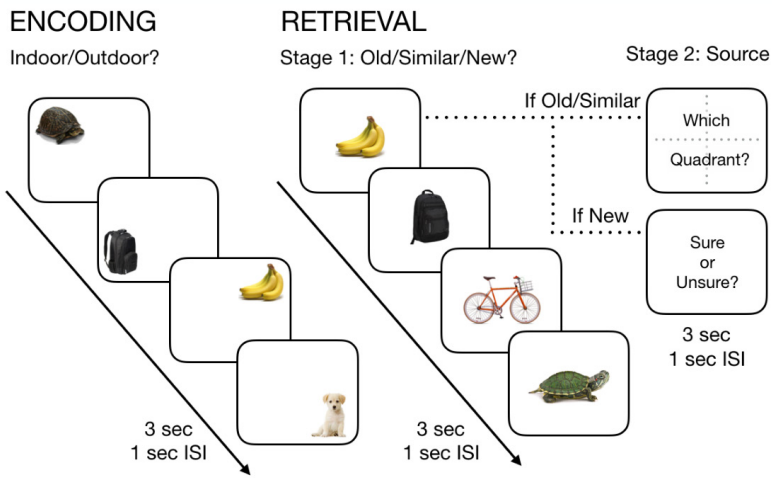
661

662 **Figure 4.** Dissociated neocortical pattern separation and source memory signals. Activity in the
663 right PRC (A) was greater for correct rejections, consistent with a pattern separation signal.
664 Activity in the right PHC (B) and bilateral angular gyrus (C,F) was greater for correct source
665 judgements, consistent with a source memory signal. Activity in the left PHC (E) showed a
666 response profile that was not consistent with predicted pattern separation or source memory
667 signals or an interaction between the two. When target hits were included in the analysis, an
668 effect of both item memory and source was observed in this region, with increased activity for
669 LCR and for incorrect source judgments. The dotted rectangle indicates conditions that were
670 included in the 2-way ANOVA. Foil correct rejections were used as baseline. Error bars indicate
671 s.e.m. SUB: subiculum. PRC: perirhinal cortex; PHC: parahippocampal cortex.

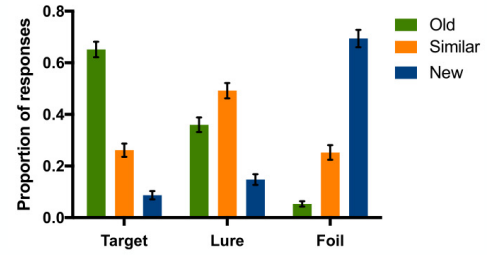
672

673 **Figure 5.** Voxelwise analysis. We ran a repeated measures ANOVA with lure discrimination
674 (lure correct rejection and false alarm) and source memory (source correct and source
675 incorrect) as fixed factors. Clusters of voxels that showed a main effect of lure discrimination are
676 colored red, clusters that showed a main effect of source are colored blue, and voxels that
677 showed a main effect of both lure discrimination and source are colored green.

A



B



C

