Holistic recollection via pattern completion involves hippocampal subfield CA3

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1   Holistic recollection via pattern completion involves hippocampal subfield CA3

2   Running Title: Holistic recollection involves subfield CA3

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31   Abstract

32

33   Episodic memories typically comprise multiple elements. A defining characteristic of episodic

34   retrieval is holistic recollection, i.e. comprehensive recall of the elements a memorized event

35   encompasses. A recent study implicated activity in the human hippocampus with holistic recollection

36   of multi-element events based on cues (Horner, Bisby, Bush, Lin, & Burgess et al., 2015). Here, we

37   obtained ultra-high resolution functional neuroimaging data at 7 Tesla in 30 younger adults (12

38   female) using the same paradigm. In accordance with anatomically inspired computational models

39   and animal research, we found that metabolic activity in hippocampal subfield CA3 (but less

40   pronounced in dentate gyrus) correlated with this form of mnemonic pattern completion across

41   participants. Our study provides the first evidence in humans for a strong involvement of

42   hippocampal subfield CA3 in holistic recollection via pattern completion.

43

44   Significance Statement

45

46   Memories of daily events usually involve multiple elements, while a single element can be

47   sufficient to prompt recollection of the whole event. Such holistic recollection is thought to require

48   reactivation of brain activity representing the full event from one event element ('pattern

49   completion'). Computational and animal models suggest that mnemonic pattern completion is

50   accomplished in a specific subregion of the hippocampus called CA3, but empirical evidence in

51   humans was lacking. Here, we leverage the ultra-high resolution of 7 Tesla neuroimaging to provide

52   first evidence for a strong involvement of the human CA3 in holistic recollection of multi-element

53   events via pattern completion.

54

55   Introduction

56

57   Episodic memories bind multiple elements into a single representation. Recollection may be

58   triggered by any one of these elements. Asked, for example, about whether we had been to a certain

59   restaurant before, we may recall meeting a friend there lately. Remarkably, the "restaurant" cue may

60   even initiate *holistic* recollection: Another guest's dog or the piano in the restaurant may come to our

61   mind. Holistic recollection thus refers to comprehensive recall of the elements an event

62   encompasses, even though incidental to the current situation (Tulving, 1983).

63   Successful pattern completion is considered a prerequisite for such holistic recollection. The

64   cue information needs to be completed towards the full event to produce comprehensive recall

65   (Marr, 1971; McClelland, McNaughton, & O'Reilly, 1995; Treves & Rolls, 1994). A corresponding

66   feature of recollective experiences is the reinstatement of the encoding-related cortical activity

67   (Bosch, Jehee, Fernández, & Doeller, 2014; Gordon, Rissman, Kiani, & Wagner, 2014; Liang & Preston,

68   2017; Staresina, Cooper, & Henson, 2013; Staresina, Henson, Kriegeskorte, & Alink, 2012). Recently,

69   it has been shown that cortical reinstatement of incidentally recalled event elements is related to

70   functional activity in the hippocampus (Horner, Bisby, Bush, Lin, & Burgess, 2015). However, the

71   spatial resolution was not sufficient to dissect the specific involvement of hippocampal subfields.

72   Anatomically inspired computational and theoretical models attribute different information

73   processing mechanisms to different hippocampal subfields. Unique recurrent collaterals in subfield

74   CA3 provide an effective condition for the implementation of pattern completion (Marr, 1971; Treves

75   & Rolls, 1991). Consequently, computational models suggest subfield CA3 to guide the incidental

76   recall of additional event elements based on pattern completion (McClelland et al., 1995; Treves &

77   Rolls, 1994).

78   Empirical support for the functional role of CA3 in pattern completion mainly originates from

79   animal research (Fellini, Florian, Courtey, & Roullet, 2009; Gold & Kesner, 2005; Lee & Kesner, 2004;

80   Nakazawa et al., 2002; Neunuebel & Knierim, 2014; Vazdarjanova & Guzowski, 2004). Until recently

4

81   the resolution of human functional magnetic resonance imaging (fMRI) did not allow to separate

82   subfield CA3 from dentate gyrus (DG). Therefore, most fMRI studies indiscriminately attribute

83   pattern completion to human subfield CA3/DG (Chen, Olsen, Preston, Glover, & Wagner, 2011;

84   Dudukovic, Preston, Archie, Glover, & Wagner, 2011; Hindy, Ng, & Turk-Browne, 2016; Schapiro,

85   Kustner, & Turk-Browne, 2012). Solely Bonnici et al. (2012) and Chadwick, Bonnici, & Maguire (2014)

86   demonstrated a generalization function selectively in CA3. Evidence for explicit functional

87   engagement of (the human) CA3 in holistic recollection and thus mnemonic pattern completion is

88   still pending.

89   Here, we aimed to provide first empirical evidence at the hippocampal subfield level for the

90   functional underpinnings of holistic recollection via pattern completion in humans using fMRI data

91   with ultra-high resolution at 7 Tesla. We used the same task as Horner and colleagues (2015) during

92   which multi-element events were learned as overlapping pairs of associations between elements

93   (places, people and objects), and subsequently retrieved as paired associations. This task allowed us

94   to assess holistic recollection both behaviorally and in terms of neural activity. That is, we calculated

95   the statistical dependency in performance of retrieving one association from an event on retrieving

96   another association from the same event. We also measured the extent of incidental retrieval of

97   event elements that were neither the cue nor target of retrieval in terms of regional activity during

98   retrieval corresponding to the nontarget element category (e.g. place, people or object). Fully

99   overlapping associations (closed-loops), which appear to create coherent events with holistic

100   recollection, were compared with partially overlapping associations (open-loops), see Horner et al.

101   (2015) for details. We hypothesized that cortical reinstatement of incidental elements during holistic

102   recollection would be associated with activity in hippocampal subfield CA3 but not DG.

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5

104   Methods

105

106   Participants

107   In total, 30 participants (12 female, mean (SD) age: 27 (4)) were recruited from the campus of

108   Otto-von-Guericke University Magdeburg and the Leibniz Institute for Neurobiology Magdeburg. All

109   participants reported to be right-handed and without any neurological or psychiatric illness. If

110   necessary, vision was corrected to normal. Minimum educational level of all participants was the

111   German Abitur (A-level). The participants received an allowance of 30 €. The study was approved by

112   the local Ethics Committee of the Otto-von-Guericke University Magdeburg.

113

114   Materials and Procedure

115   Regarding materials and procedure we follow Horner et al.'s, (2015) set up closely. In the

116   following sections the main features of the design are outlined and adjustments that were necessary

117   are specified.

118

119   *Materials*

120   Stimuli consisted of written words that belonged to four categories: locations (e.g. kitchen),

121   objects (e.g. hammer), animals (e.g. mouse) and famous people (e.g. Obama). The words were taken

122   from Horner et al. (2015) and translated into German. To assure a similar level of familiarity within

123   our German sample, several people-stimuli were changed based on preceding behavioral pilot

124   results. In total, 36 events were created by associating one example out of each category with

125   another. Initially, four event sets were built and randomized across participants. For each participant,

126   18 events were assigned randomly to consist of four categories (location – object – people – animal).

127   These events will be referred to as open-loop structure events in the following. The remaining 18

128   events consisted of three categories. Within these closed-loop structure events, 9 events were

129   randomly selected to encompass the categories location – object – people and 9 events to

130   encompass the categories location – animal – people.

131   Words were presented in white font on a black background to the center of a screen (font

132   size = 30) and via a mirror mounted on the head coil, participants could watch the projected screen

133   with a visual angle of +/- 3° x +/- 2 °.

134

135   *Task Procedure*

136   Prior to the scanning session, participants received task instructions. The task was described

137   as an associative learning paradigm. They were told to imagine each displayed associative word pair

138   together in one scene as vividly as possible. Importantly, the underlying associative event structure

139   of the stimuli was not revealed and remained implicit.

140   During the scanned encoding phase, participants learned the 36 events in a pair-wise

141   associative manner. The encoding phase consisted of three blocks with 36 trials each, adding up to a

142   total of 108 encoding trials. In each block, one associative pair of each event was presented for 6

143   seconds (e.g. kitchen – hammer out of the event kitchen – hammer – Obama – dog, Figure 1C).

144   Following that procedure, one element within an event overlapped between the first and the second

145   encoding block. At the third block, some events remained as an associative chain and followed an

146   "open-loop" event structure (Figure 1B). Thus, in the last encoding block, the third associative pair

147   from these events overlapped again with one element from previously encoded associates of the

148   respective event (AB – BC – CD). In contrast, "closed-loop" events were structured such that at the

149   last encoding block both elements of the currently encoded associate overlapped with previously

150   encoded elements from the respective event (AB – BC – CA; Figure 1A).

151   The specific category pairing at each block was randomized. However, the third encoding

152   block was restricted to a location – object/animal or a people – object/animal category pair. Further

153   details about the randomization procedure can be found in Horner et al. (2015). No responses were

154 required by the participants. The interstimulus interval was 1500 ms and each encoding trial was

155 initiated with a fixation cross of 500 ms.

156   The scanned retrieval phase followed encoding immediately. Here, each pairwise association

157 within an event was tested. This yielded 6 retrieval trials per event and 215 retrieval trials in total.

158 The 6 retrieval trials were distributed over 6 blocks. During each block one associative pair from each

159 event was tested - each pair bidirectionally. On each trial, participants were cued with one element

160 from an event and instructed to retrieve an associated element by means of a 4-alternative forced

161 choice recognition procedure (Figure 1D). The displayed lures belonged to the same category as the

162 target but were taken from other encoded events. Cue and response options were presented until a

163 response was made but with a maximum of 6 seconds. See Horner et al., 2015 for further details on

164 the randomization procedure at retrieval. Each retrieval trial was followed by a $1 – 4$ confidence

165 rating for 6 seconds. The interstimulus interval was 1500 ms and each retrieval trial was initiated

166 with a 500 ms fixation cross.

167   A debriefing phase of approximately 30 min immediately followed the scanning session.

168 More details regarding the administered questions can be found in Horner et al. (2015).

169   *--- Figure 1 ---*

170

171 *Scanning procedure*

172   The scanning was performed with a 7 Tesla MRI Siemens machine. A 32-channel head coil

173 was used. Participants received earplugs and ear defenders to protect against noise. Prior to

174 functional data acquisition, structural images were acquired. First, a whole-brain T1-weighted

175 volume was obtained (TR = 2300 ms; TE = 2.73 ms; flip angle = 5°; resolution = 0.8 mm isotropic;

176 matrix size = 320 x 320). Second, a partial high-resolution T2-weighted volume was acquired with an

177 orientation aligned orthogonally to the hippocampal main axis (TR = 8000 ms; TE = 76 ms; slice

178 thickness = 1 mm with 1.1 mm slice spacing; in-plane resolution = 0.4375 mm x 0.4375 mm; 55

179 coronal slices; FOV = 256 mm x 256 mm; matrix size = 512 x 512).

180   Succeeding the structural data acquisition, two runs of functional data were obtained. Both

181   runs consisted of T2*-weighted echo planar slices (EPI), oriented in parallel to the hippocampal long

182   axis (28 axial slices; TR = 2000 ms; TE = 22ms; matrix size 1536 x 1536; FOV = 256mm x 256 mm;

183   resolution= 0.8 mm, odd-even interleaved slice acquisition). First, functional data regarding the

184   encoding phase was obtained (440 volumes). Second, the functional data regarding the retrieval

185   phase was obtained (approximately 700 volumes, depending on response times). Responses were

186   recorded using a scanner-compatible 4-choice button box. The complete scanning procedure took

187   approximately 80 min.

188   The functional data was distortion corrected by means of a point spread function (Zaitsev,

189   Hennig, & Speck, 2004) and online motion corrected during image reconstruction.

190

191   Behavioral Data Analyses

192   The overall accuracy per participant was calculated as the percentage of correct retrieval

193   trials. Note that there are 6 retrieval trials for each of the 36 events. We calculated accuracy

194   separately for closed- and open-loop events. With a paired samples t-test, we tested for significant

195   differences in performance between loop conditions (closed- versus open-loop events). We also

196   evaluated the amount of retrieval dependency among the elements within an event, separately for

197   closed- and open-loop events. This measure reflects the likelihood that an element is successfully

198   retrieved, given successful retrieval of the other elements that belong to the same event. The

199   dependency measures were calculated by means of participant-specific contingency tables. In total,

200   six contingency table were created per participant, one for each category (location (A), people (B),

201   object (C)) being either cue or target. The cue-based tables reflect the retrieval dependency of two

202   elements from the same event across separate retrieval trials, given the trials used the same cue

203   element from the respective event (AbAc). The target-based tables reflect the retrieval dependency

204   of the same target element across separate retrieval trials, given the trials used different cue

205   elements belonging to the same event (BaCa). Each table's cells contain the retrieval performance

9

206   across events for the respective condition. The dependency measure based on observed data is

207   defined as the proportion of events for which both overlapping associations related to a common

208   element (either being cue or target) are retrieved successfully or unsuccessfully.

209   To assess the dependency measures from the data, we compared them with both a model

210   that assumes full retrieval dependency, and a model that assumes full retrieval independency among

211   all elements of an event. The expected dependency based on the independent model was estimated

212   by multiplying the probabilities of separately retrieving either of the two items of an event within the

213   contingency tables. The dependent model is based on the independent model but estimates the

214   expected dependency by accounting for the level of guessing and inserting an "episodic factor". This

215   "episodic factor" weights the performance for a certain event by a factor that captures the difference

216   between the respective event's performance across separate retrieval trials versus general

217   performance across all events. Note, that the measure of observed dependency scales with accuracy.

218   Therefore, only comparisons between observed dependency measures and model-based expected

219   dependency values are informative. Comparisons between dependency measures were made using

220   paired-samples t-tests for both event structure conditions (open-loop and closed-loop), separately.

221   For further details on the calculation of dependency measures based on the data and based on the

222   two models, see Horner et al. (2015) and Horner & Burgess (2013).

223   To gain an impression of dependency differences that might be masked due to high accuracy

224   levels in both loop conditions (88.55% and 86.27% for closed- and open-loop, respectively), the

225   confidence level was taken into account. Dependency measures were evaluated in the above

226   described manner. However, instead of calculating dependency measures based on contingency

227   tables that refer to correct versus incorrect retrieval, now the contingency tables were refined to

228   reflect high confidence (score 4 or 3) versus low confidence (score 1 or 2) or incorrect retrieval.

229   Statistical comparisons between dependency scores in different event loop conditions were made

230   with paired-samples t-test. As indicated above, these comparisons involve the differences in

231   observed dependency and expected dependency based on the independent model in respective

232   conditions.

233

234   Functional Data Analyses

235   *Preprocessing*

236   All preprocessing steps were performed with SPM12 (Statistical Parametric Mapping, Version

237   12, Wellcome Trust Centre for Neuroimaging, University College London; RRID:SCR_007037; Penny,

238   Friston, Ashburner, Kiebel, & Nichols, 2011). The raw functional data was distortion and motion

239   corrected already (see fMRI acquisition). First, the raw data was converted from DICOM into NifTi

240   format. Second, slice timing correction was applied and the data was smoothed with a full-width

241   half-maximum Gaussian kernel of 2x2x2 mm. The size of the kernel was chosen based on previous

242   reports to preserve high specificity but increase sensitivity at the same time (Berron et al., 2016;

243   Maass, Berron, Libby, Ranganath, & Düzel, 2015).

244   Outliers based on motion (threshold 2 mm) or global signal (threshold 9.0) were detected by

245   the ARTifact detection Tools (ART) software package (RRID:SCR_005994; Mozes & Whitfield-Gabrieli,

246   2011). The fully preprocessed data was used for outlier detection. The procedure resulted in a vector

247   for each participant that indicated outlier scans. They were entered as separate regressors into all

248   univariate analyses (see below).

249

250   *Structural template calculation (T1 weighted)*

251   To calculate and visualize functional analyses results on group level, a sample-specific

252   template was created for the T1-weighted structural volumes. This assures optimal alignment of the

253   functional data across participant (Avants et al., 2011). We used the nonlinear diffeomorphic

254   mapping procedure called "buildtemplateparallel.sh" provided by Advanced Normalization Tools

255   (ANTS) to construct a T1-template based on the 30 whole-brain T1-weighted volumes obtained from

256   all participants (RRID:SCR_004757; Avants et al., 2010).

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258

259   *Hippocampal segmentation*

260   The current study aimed to examine specific functional activity patterns in the hippocampus.

261   Thus, we restricted several functional analyses (indicated below) to hippocampal regions of interest

262   (ROI). Using ITK-SNAP (RRID:SCR_002010; Yushkevich et al., 2006) we manually segmented the

263   bilateral hippocampus in all 30 participants on their specific T2-weighted structural volume. Therein

264   we followed the segmentation protocol by Berron et al. (2017). This yielded participant-specific

265   masks for HC subfields CA1, CA2, CA3, Subiculum and DG, one for each hemisphere.

266   To use these masks as anatomical regions of interests in the functional analyses, each

267   participant-specific T2-weighted HC subfield mask was coregistered to the participant's EPI-space

268   and resampled to the EPI-resolution. This was accomplished in two steps. First, SPM12 was used to

269   coregister and resample the T2-weighted HC subfields masks to the individual T1 space by applying

270   "spm_coreg" (Penny et al., 2011). Second, these masks where coregistered from the individual T1

271   space to the EPI space using FSL FLIRT (RRID:SCR_002823; Greve & Fischl, 2009; Jenkinson, Bannister,

272   Brady, & Smith, 2002; Jenkinson & Smith, 2001). See Figure 2 for an example segmentation and

273   coregistration from T2 to EPI space.

274   All masks were divided in an anterior and a posterior part. To that end, the main

275   hippocampal extension in each hemisphere was defined for each individual by taking the outer parts

276   of the z-dimension. All hippocampal subfields of that participant within that hemisphere were split in

277   two at the border identified by half the length of the total hippocampus in z direction.

278   *--- Figure 2 ---*

279

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283   *General functional analyses approach*

284   All functional analyses were performed with SPM12 (Statistical Parametric Mapping, Version

285   12, Wellcome Trust Centre for Neuroimaging, University College London; Penny et al., 2011)) on

286   single participant and group level.

287   *Functional analysis at the participant level.* At the first level, a general linear model was fit to

288   each participant's functional data in native space. Therefore, the underlying neural data was

289   modelled by a boxcar function at stimulus onset for each condition of interest (dependent on the

290   respective analysis). The resulting neural model was convolved by a canonical hemodynamic

291   response function to predict the functional data. Besides the regressors predicting the functional

292   data related to each condition of interest, each general linear model also included one intercept

293   regressor and six motion correction parameters as regressor of no interest. The motion-correction

294   parameters were added to capture variability related to task-correlated motion and reduce the

295   amount of false-positive activity in task conditions (Johnstone et al., 2006). If applicable, a regressor

296   of no interest was added to capture variance in the functional data related to the outlier scans. Each

297   general linear model was fit to the acquired functional data to obtain parameter estimates for each

298   condition of interest. To examine differences in BOLD activity related to the conditions of interest,

299   contrast maps were calculated for each participant in native space (specific contrasts dependent on

300   respective analysis).

301   *Normalization.* To be able to assess consistent contrast effects at group level, we normalized

302   each participant's contrast maps to the group T1 template. Therefore, we first normalized each

303   participant's mean functional echo-planar image to the participant's structural T1 image and then to

304   the T1 group template by using FSL "epi_reg" (Greve & Fischl, 2009; Jenkinson et al., 2002; Jenkinson

305   & Smith, 2001) and ANTS "WarpImageMultiTransform.sh" respectively (Avants et al., 2010, 2011).

306   This procedure resulted in participant-specific transformation matrices that could then be used for

307   the spatial normalization of the contrast maps.

13

308   *Second level group analyses.* For group analyses, we assessed consistent differences in

309   functional activity across participants. Therefore, the spatially normalized contrast maps from each

310   participant were entered into a general linear model using SPM12 (Penny et al., 2011). Unless stated

311   otherwise, group results are reported with an initial cluster defining threshold of *p* <.005.

312

313   Functional analyses in detail

314   Two participants were excluded from all functional analyses due to an amount of outlier

315   scans exceeding 10 % of the total scans at retrieval. Outliers were determined by excessive motion

316   (threshold 2 mm) or global signal changes (threshold 9.0). In addition, all region-of-interest analyses

317   within hippocampal subfields were conducted with one participant less due to motion in the T2

318   image of that participant which made hippocampal subfield segmentation impossible.

319   For all analyses the object and animal conditions were merged (see Horner et al., 2015).

320   Note, that we did not see any specific functional activity for animals in the 'retrieval phase – element

321   specific activity' analysis (see below). When lowering the threshold (p < .005, uncorrected), however,

322   functional clusters were comparable to the object condition (in lateral occipital cortex). As we did not

323   see differences in functional activity, we collapsed object and animal conditions to assure

324   comparability of results with Horner et al. (2015). The animal and the object condition will both be

325   referred to as the object category in the following.

326

327   *Retrieval phase – element specific activity*

328   To examine significant clusters of functional activity related to specific categories of event

329   elements, we set up a general linear model with 7 regressors of interest. Each regressor included the

330   boxcar convolved stimulus onsets for one type of cue-target association (location – object; object –

331   location; object – people; people – object; people – location; location – people). Each trial duration

332   was determined by the response time. An additional regressor was included that modelled the

333   interstimulus interval with a duration of 1.5 seconds. To assess differences in functional activity

14

334   related to the three element categories, contrast maps were obtained between the parameter

335   estimates related to the regressors that contained the respective category and those that did not

336   contain the respective category. For instance, to obtain location related clusters of significant

337   functional activity, we contrasted the parameter estimates obtained for the location-object, object-

338   location, location-people and people-location regressors with the parameter estimates for the

339   object-people and people-object regressors.

340   To examine consistent clusters of significant functional activity at group level, the normalized

341   contrast maps were entered into a one sample t-test on second level. All results are reported with

342   family-wise error correction after applying an initial cluster defining threshold of $p <.001$.

343

344

345   *Cortical reinstatement at retrieval*

346   Here, we initially evaluated whether the function an element occupies at retrieval (cue,

347   target or nontarget) entails differences in the overall amount of cortical reinstatement.

348   Subsequently, differences in cortical reinstatement of cues, targets and nontargets between closed-

349   and open-loop events were explored.

350   To begin with, the amount of cortical reinstatement was assessed for each function an

351   element could take (cue, target and nontarget), across event loop conditions. This yielded an overall

352   cortical reinstatement score per element function and participant (Figure 3A). Based on the previous

353   analysis (retrieval phase - element specific activity) we obtained a significant cortical functional

354   cluster for each category (location, people and object) at the group level (Figure 3A(ii)). In the case of

355   multiple significant functional clusters, we focused on the element-specific ROI that was identified by

356   Horner et al. (2015) to assure comparability of results (note that we obtained comparable results

357   when using all our identified clusters). The corresponding functional masks were coregistered to each

358   participant's native space with FSL FLIRT (Greve & Fischl, 2009; Jenkinson et al., 2002; Jenkinson &

359   Smith, 2001). Using REX (RRID:SCR_005994; Whitfield-Gabrieli, 2009), we then extracted participant-

360 specific parameter estimates for each regressor of interest in the element specific activity analysis

361 out of each element-specific ROI. Parameter estimates within each ROI were z-standardized. To

362 obtain a participant specific value for the amount of cortical reinstatement related to each element

363 function, we took the parameter estimates out of each ROI, first for the condition that the respective

364 ROI was related to the category of the cue ("cue cortical reinstatement"), second for the condition

365 that the respective ROI was related to the category of the target ("target cortical reinstatement"),

366 and third for the condition that the respective ROI was neither related to the category of the cue or

367 the target but only related to the nontarget category ("nontarget cortical reinstatement", Figure 3A).

368 For instance, the previous analysis (element-specific activity at retrieval) found a significant cluster of

369 increased functional activity in the parahippocampal cortex for location category stimuli. Now, we

370 took the parameter estimate regarding the people-object and object-people condition out of the

371 parahippocampal cortex to obtain a measure for the nontarget cortical reinstatement for when the

372 location was nontarget. Similarly we proceeded for the remaining two categories (people, object) to

373 obtain nontarget cortical reinstatement values for each category. The normalized parameter

374 estimates were averaged across ROIs (i.e. categories) for each participant, separately for cue, target

375 and nontarget cortical reinstatement (Figure 3A(iii)). Differences in the amount of overall cortical

376 reinstatement between element functions (cue, target, nontarget) were tested using a repeated

377 measures ANOVA.

378   To further explore the differences in cortical reinstatement between closed- and open-loop

379 events, we then evaluated cortical functional activity for both event loop conditions. To compare

380 cortical reinstatement between event loop conditions, we had to delineate functional cortical activity

381 for closed- and open-loop events. Therefore, the above described univariate analysis (element-

382 specific activity at retrieval) was performed again. Instead of 7 regressors of interest, 14 were

383 created, they contained the same information as the 7 in the analysis before, now split up into trials

384 that belonged to closed-loop and open-loop events. Then, the same procedure was followed as

385 described above to acquire element-related cortical activity values for cue, target and nontargets per

386   participant. Now however, calculated for closed-loop events and open-loop events separately.

387   Subsequently, obtained difference scores for cortical reinstatement between event loop conditions

388   were tested for significant deviation from zero by using one-sample t-tests to assess whether cortical

389   reinstatement was higher in closed-loop events.

390

391   *Hippocampal activity and cortical reinstatement*

392   The following analyses were aimed to identify activity clusters in the hippocampus that

393   functionally relate to holistic recollection and to delineate their subfield-specific localization. As

394   holistic recollection is conceptualized to be measurable by the amount of nontarget cortical

395   reinstatement, we assessed hippocampal functional correlates of increased nontarget cortical

396   reinstatement in closed-loop events.

397   We first followed an exploratory parametric analysis approach to assess whether any

398   hippocampal cluster correlates with nontarget cortical reinstatement under conditions of increased

399   holistic recollection. Therefore, initially a univariate first level analysis was performed. The general

400   linear model encompassed three regressors of interest. One contained the boxcar function

401   convolved stimulus onsets for trials that are part of closed-loop events (duration equaled response

402   time). The second regressor contained the boxcar function convolved stimulus onsets for trials that

403   belong to open-loop events (duration equaled response time). The third regressor contained the

404   boxcar convolved onsets of the inter stimulus intervals (duration 1.5 seconds). Contrast maps were

405   obtained for each participant for closed-loop versus open-loop event retrieval trials.

406   To investigate hippocampal involvement in holistic recollection, that is particularly the

407   cortical reinstatement of nontargets, we used the first level contrast maps that indicated for each

408   individual where in the hippocampus BOLD activity was greater for closed-loop than open-loop event

409   retrieval (Figure 3B). With the second level group analysis, we investigated which of the functional

410   activity clusters that related to closed-loop retrieval correlate with the amount of nontarget cortical

411   reinstatement across participants (Figure 3B). To assess the functional specificity of the revealed

17

412   significant cluster at nontarget cortical reinstatement, the second level group analysis was performed

413   two more times, additionally for cue cortical reinstatement and target cortical reinstatement. Each

414   general linear model included the normalized contrast maps for the contrast closed > open-loop

415   retrieval of each participant as a first regressor. The second regressor included the respective

416   participant-specific value for cue, target or nontarget reinstatement, obtained by the independent

417   analysis of element-category related cortical activity at retrieval (Figure 32A). All results are reported

418   with an initial cluster defining threshold of p < .005. Small volume correction with a bilateral

419   hippocampal mask was applied at second level.

420   To assess whether the identified hippocampal cluster correlated more with nontarget cortical

421   reinstatement than with cue or target reinstatement, participant-specific mean functional activity

422   was extracted from the respective cluster for the contrast closed > open-loop retrieval with REX

423   (Whitfield-Gabrieli, 2009). Pearson correlation coefficients for each cortical reinstatement type (cue,

424   target and nontarget) with the extracted functional cluster activity were obtained. With a one-tailed

425   z-test we tested whether the obtained Pearson correlation coefficients were significantly higher for

426   nontarget reinstatement than for cue and target reinstatement respectively (Diedenhofen & Musch,

427   2015; Rosenthal, Rubin, & Meng, 1992).

428   The clusters identified by above described analyses can only be attributed to a specific

429   subfield by visual inspection. As they were considered to be located close to the right anterior CA3-

430   DG border, a subsequent region-of-interest analysis was performed to delineate functional

431   involvement of CA3 versus DG. Therefore, mean beta values from the first level analyses were

432   extracted using REX (Whitfield-Gabrieli, 2009) for each individual out of the manually segmented

433   hippocampal subfields masks for right anterior CA3 and right anterior DG. Beta values were extracted

434   referring to the closed-loop regressor and to the open-loop regressor. Pearson correlation

435   coefficients and corresponding significance values were obtained for the relationship between the

436   difference in beta values (closed- versus open-loop) and the amount of nontarget reinstatement

437   across participants. With a one-tailed z-test we tested whether the obtained Pearson correlation

18

438   coefficient was significantly higher for right anterior CA3 than right anterior DG (Diedenhofen &

439   Musch, 2015; Rosenthal et al., 1992).

440   *--- Figure 3 ---*

441

442   Results

443

444   Behavioral Results

445   On average 87.41% (SD = 9.78%) of all trials in the recall phase were answered correctly by

446   the 30 participants. There was no significant difference in accuracy between closed-loop (mean =

447   88.55%, SD = 8.96%) and open-loop events (mean = 86.27%, SD = 10.60%).

448   We also investigated the amount of dependency among event elements. Note, that the

449   dependency measure we calculated scales with accuracy. Therefore the evidence for dependency is

450   defined as the difference between data-based dependency and the expected dependency based on

451   the independent model. The evidence for dependency is not significantly higher for closed- than

452   open-loop events ($t(29)$ = 1.162; p = .255). The higher the overall accuracy, the more dependency

453   values approach 1 (also see Horner et al., 2015). Our very high accuracy may thus have led to ceiling

454   levels in the estimated dependency measures, making it impossible to detect differences between

455   open- and closed-loop event dependency.

456   To test whether the high overall accuracy may have obscured stronger dependency among

457   closed-loop elements, we calculated dependency again by taking the confidence level into account.

458   That is, instead of classifying the retrieval trials by correct versus incorrect, we split them into high

459   and low confidence trials and collapsed incorrect and low confidence trials. The evidence for

460   dependency is not significantly different between loop conditions ($t(29)$ = 1.978; p = .058). However,

461   open-loop events but not closed-loop events showed significantly lower dependency than the

462   dependent model ($t(29)$ = -2.59; p = .015 and $t(29)$ = -1.47; p = .152). Numerically, our results are

463   consistent with previous results (Horner et al., 2014; Horner et al., 2015). That is, retrieval at closed-

464   loop events entails more dependency among event elements than retrieval at open-loop events

465   (Figure 4).

466   --- *Figure 4* ---

467

468   Univariate Results

469   *Element-specific cortical activity at retrieval*

470   The aim of this analysis was to identify element-specific cortical functional activity patterns at

471   retrieval. Therefore, category associations that contained a respective element were contrasted with

472   category associations that did not contain the respective element (e.g. identify location activity by

473   contrasting location – object and location – people with people – object trials).

474   People-related activity was found in the medial parietal lobe (cluster size k = 1172, *p* < .001,

475   see Figure 3A(i)), in a left inferior temporal cluster (cluster size k = 103, *p* = .006) and in a right lateral

476   parietal cluster (cluster size k = 126, *p* = .001). Object-related activity was found in the left lateral

477   occipital lobe (separated into three clusters, first cluster size k = 864, *p* < .001 , see Figure 3A(i);

478   second cluster size k = 101, *p* = .006, third cluster size k = 75, *p* = .041). Location-related activity was

479   found in bilateral clusters in the parahippocampal cortex (left cluster size k = 2242, *p* < .001, right

480   cluster size k = 883, *p* < .001, see Figure 3A(i)), bilateral retrosplenial cortex (cluster size k = 7786, *p* <

481   .001) and bilateral lateral parietal cortex (left cluster size k = 698, *p* < .001, right cluster size k = 418, *p*

482   < .001).

483

484   *Cortical reinstatement during closed-loop event retrieval*

485   The identification of element-specific activity patterns at retrieval allowed us to obtain

486   participant-specific values for the amount of cortical reinstatement at retrieval (Figure 3A).

487   Therefore, parameter estimates were extracted from each element-specific cortical region when the

488   respective element functioned as a cue, target or nontarget. We averaged these values across

489   element categories. Note that, when multiple element-specific clusters have been identified, we

490   extracted parameter estimates exclusively from the region selected by Horner et al. (2015) to assure

491   comparability of results (i.e. people: medial parietal cluster, animal/object: left lateral occipital

492   cluster, location: bilateral parahippocampal cluster). Thus, we obtained three values per participant

493   that reflect the element-related cortical activity at retrieval: First, the cue cortical reinstatement,

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494   thus the functional cortical activity induced by cues, second, the target cortical reinstatement, that is

495   functional cortical activity induced by targets and third, the cortical reinstatement of nontargets, i.e.

496   the cortical reinstatement of event elements currently incidental to the task.

497   Over all experimental conditions, cue and target cortical reinstatement was significantly

498   higher than nontarget cortical reinstatement, and targets induced significantly more cortical activity

499   than cue elements (Figure 5A; main effect of element function $F(2,75) = 111.35$; $p < .001$, ANOVA).

500   Note that the displayed beta values are not in relationship to an explicit baseline but rather the

501   overall mean parameter estimate. Differences are thus not absolute but relative to each other. We

502   operationalized holistic recollection as the amount of incidental reinstatement, i.e. reactivation

503   corresponding to nontarget elements. To test whether closed-loop event retrieval entails more

504   holistic recollection, we investigated whether more nontarget cortical reinstatement took place for

505   closed-loop than open-loop event retrieval (see Figure 3B). Indeed, the difference between the

506   amount of element-related cortical activity in closed- and open-loop conditions is only significantly

507   higher than zero for nontargets ($t(25) = 2.46$, $p = .02$), not so for cues ($t(25) = -1.04$, $p >.05$) or targets

508   ($t(25) = -.05$, $p > .05$; Figure 5B; one-sample t-tests). Thus, cortical reinstatement of nontargets was

509   higher for closed-loop than open-loop retrieval.

510   --- *Figure 5* ---

511

512   *Anterior CA3, but not DG activity during closed-loop retrieval correlates with overall nontarget*

513   *reinstatement*

514   Phenomenological differences between closed- and open-loop retrieval in terms of holistic

515   recollection, i.e. the amount of nontarget cortical reinstatement, are apparent based on the previous

516   analyses. We therefore examined whether there are specific hippocampal functional correlates of

517   closed-loop event retrieval. When functional differences between closed- and open-loop event

518   retrieval are related to holistic recollection, they should scale with the amount of nontarget

519   reinstatement a participant engages in.

520   First, we contrasted BOLD activity during closed- and open-loop event retrieval within each

521   participant. This yielded participant-specific statistical maps indicating functional activity differences

522   between both loop structures. At the group level these contrast maps were then correlated with the

523   participant-specific amount of nontarget cortical reinstatement. This explorative approach yields

524   clusters within the hippocampus that display increased functional involvement during closed-loop

525   event retrieval when overall nontarget cortical reinstatement, i.e. holistic recollection, is high (Figure

526   3B). An anterior right hippocampal cluster (cluster size k = 35; *p(cluster)* = .028 (uncorr)), located in

527   subfield CA3, was revealed that scales its functional activity during closed-loop event retrieval with

528   the participant's amount of overall nontarget cortical reinstatement (Figure 6A). Note, that no

529   significant clusters could be identified for the reverse correlation and when correlating individual

530   contrast maps for open > closed-loop retrieval with the overall nontarget cortical reinstatement

531   across individuals.

532   To test whether the identified cluster was specific for nontarget reinstatement, i.e. holistic

533   recollection, and not related to other retrieval processes, we first tested whether the respective

534   cluster correlated with cue and target reinstatement as well. Pearson correlations between cluster

535   activity (i.e. extracted beta values for the closed – open-loop contrast) and cue as well as target

536   reinstatement were significantly lower than the previously identified correlation of the right anterior

537   CA3 cluster with nontarget reinstatement (z = -2.584, p = .005 and z = -3.226, p = .001 for the

538   difference in correlations between p(nontarget reinstatement, cluster activity) and p(cue

539   reinstatement, cluster activity) or p(target reinstatement, cluster activity), respectively). Second, we

540   investigated whether additional anterior hippocampal activity is related to cue or target induced

541   cortical activity. Therefore, the same parametric analyses approach was adopted at group level as we

542   applied for the identification of hippocampal activity related to nontarget reinstatement. Now,

543   however we correlated the difference in functional activity between loop conditions with cue and

544   target cortical reinstatement respectively. No anterior hippocampal cluster showed increased

545   involvement during closed-loop event retrieval with higher amounts of cue or target cortical

546   reinstatement.

547   Taken together, we identified a cluster, located in anterior right hippocampal subfield CA3,

548   where activity during closed-loop retrieval correlates with the amount of overall nontarget cortical

549   reinstatement in each participant.

550   *--- Figure 6 ---*

551   So far, only by visual inspection we assigned the identified right anterior hippocampal cluster

552   to subfield CA3. As the cluster is in close vicinity to the DG, we aimed to disentangle the specific

553   contributions. Therefore, a region-of-interest approach was adopted. We extracted functional

554   activity (beta values) from manually segmented right anterior subfield CA3 and DG respectively for

555   the loop condition contrast (closed > open-loop event retrieval). The mean functional activity within

556   ROIs was correlated with the amount of nontarget cortical reinstatement across participants. Indeed,

557   only for the right anterior CA3 but not for the right anterior DG the mean functional activity was

558   correlated with the overall amount of nontarget cortical reinstatement across participants (Figure 7;

559   R^2 = 0.16, p = 0.049 and R^2 = 0.04, p = 0.355 for the correlation nontarget cortical reinstatement –

560   right anterior CA3 and DG, respectively). The correlation between nontarget cortical reinstatement

561   and right anterior CA3 was, however, not significantly higher than with right anterior DG (z = 1.088, p

562   = .138). The region-of-interest results are further evidence for a trend towards specific functional

563   involvement of subfield CA3 (right anterior) but less of adjacent subfield DG in closed-loop event

564   retrieval when participants generally entail more nontarget cortical reinstatement.

565   *--- Figure 7 ---*

566

567   Discussion

568

569   Using ultra-high resolution 7 Tesla fMRI, we provide first empirical evidence for the

570   involvement of human hippocampal subfield CA3 in holistic recollection via pattern completion.

571   Therein we go beyond a replication of the main findings by Horner et al. (2015) and unpack the

572   functional involvement of hippocampal subfields at recollection of multi-element events.

573   Our paradigm relies upon the assumption that multi-element events composed as a closed-

574   loop entail more holistic recollection at retrieval than events with an open-loop structure. Extensive

575   previous research provides support for an increased dependency among event elements that are

576   encoded in an all-to-all associative manner (Horner et al., 2015; Horner & Burgess, 2013, 2014). The

577   likelihood to incidentally retrieve event elements when cued with one element, i.e. for holistic

578   recollection is therefore increased in closed-loop events. Consequently, cortical reinstatement of

579   incidental event elements has been shown and here again been confirmed to be higher when

580   retrieving closed-loop events (Horner et al., 2015; Figure 4 and 5). We additionally demonstrated

581   increased functional involvement of right anterior subfield CA3 at closed-loop event retrieval in

582   relation to cortical reinstatement of incidental elements (Figure 6A). Our data indicate that anterior

583   CA3 activity is related to successful pattern completion associated with holistic recollection. Thereby

584   we contribute to recent efforts in empirically addressing the functional subfield architecture of the

585   human hippocampus.

586   While models of the functional organization of hippocampal subfields (Amaral & Witter,

587   1989; Hunsaker & Kesner, 2013; Lisman, 1999) have been informed by anatomical and animal

588   research, the translation of these insights to humans has been limited by the resolution of fMRI,

589   particularly in distinguishing functional activity in CA3 and DG. Here, we were able to acquire

590   functional images with a submillimeter resolution (0.8 mm isotropic) allowing us to segment CA3 and

591   DG separately and to examine specific functional patterns of both subfields (Berron et al., 2016).

592   Indeed, the anatomical ROI analysis confirms that the association between functional subfield

593   activity and the amount of holistic recollection particularly holds for anterior CA3 but less for the

594   adjacent DG (Figure 7). The association between subfield CA3 and a condition that entails more

595   pattern completion is in accordance with previous animal research (Fellini et al., 2009; Gold &

596   Kesner, 2005; Lee & Kesner, 2004; Nakazawa et al., 2002; Neunuebel & Knierim, 2014; Vazdarjanova

597   & Guzowski, 2004).

598   Despite proposed anatomical and functional heterogeneity between hippocampal subfields,

599   recent human functional imaging showed functional heterogeneity along the longitudinal axis (e.g.

600   Brunec et al., 2018; Collin, Milivojevic, & Doeller, 2015). Interestingly, proposals exist for scene

601   imagination, transitive inference processes and pattern completion being related to the anterior

602   hippocampus (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013; Strange, Witter, Lein, & Moser,

603   2014; Zeidman & Maguire, 2016). Our finding of anterior hippocampal involvement in holistic

604   recollection might be seen in line with that literature.

605   Also along the transversal axis of the hippocampus considerable heterogeneity has been

606   suggested. Importantly, the anatomical transition between subfields is not decisive but rather graded

607   (Amaral & Witter, 1989). This renders it difficult to strictly examine functional activity of CA3 and DG

608   independently. Moreover, despite the usage of ultra-high resolution functional imaging, 2 mm

609   smoothing was applied which blurs functional data at the border of segmented subfields.

610   Nevertheless, our anatomical ROI analysis averages functional signal across whole subfields that

611   extend more than the 2 mm smoothing radius. The observed significant correlation between CA3

612   activity and holistic recollection is thus, even though not completely independent from DG activity, a

613   confirmation of CA3 being significantly involved at successful holistic recollection.

614   Particularly in the anterior medial part (i.e. uncal region), hippocampal anatomy is highly

615   complex and variable between individuals (Ding & Van Hoesen, 2015). Therefore, some subfield

616   segmentation protocols decided to spare this region (e.g. Dalton, Zeidman, Barry, Williams, &

617   Maguire, 2017). Indeed, subfield specific interpretations in the hippocampal head should be drawn

618   with caution. However, the segmentation protocol, that we have applied, leveraged the higher

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619 resolution at 7T (i.e. 1 mm slice thickness) to translate recent findings on subfield boundaries in the

620 hippocampal head from neuroanatomy to MRI (Ding & Van Hoesen, 2015; Berron et al., 2017).

621   Note, that the cortical reinstatement of incidental elements ("nontargets", Figure 3) is an

622 indirect measure for hippocampal pattern completion. Theoretical models propose that successful

623 retrieval is initiated by completing a cue pattern towards the full event representation in the

624 hippocampus (Marr, 1971; McClelland, 1995; Treves & Rolls, 1994). Pattern completion may go

625 beyond the required target and include nontargets, particularly if the event representation binds

626 multiple elements tightly together (as e.g. in closed-loop events, Horner et al., 2015; Horner &

627 Burgess, 2014). The elements of the completed event representation are subsequently reinstated in

628 the cortex, which then creates a recollective experience (Bosch et al., 2014; Gordon et al., 2014;

629 Liang & Preston, 2017; Staresina et al., 2012; Staresina, Cooper, & Henson, 2013; Thakral, Wang, &

630 Rugg, 2015). Thus, our observation of increased cortical activity associated with incidental event

631 elements upon retrieval, and its correlation with activity in CA3 supports these models and implicates

632 CA3 in hippocampal pattern completion and holistic recollection.

633   Even though our measure of pattern completion is indirect, several aspects of our results

634 support the specific involvement of anterior CA3 in holistic recollection. First, the anterior CA3

635 cluster related to cortical reinstatement of nontargets could not be identified in relationship to cue

636 or target cortical activity and functional activity within the CA3 cluster was not correlated with

637 reinstatement of cues or targets (Figure 6B). As cues and targets are presented on screen, successful

638 pattern completion is less relevant for the retrieval of these elements. The increased activity of

639 anterior CA3 at closed-loop event recollection when nontarget cortical reinstatement is high, can

640 thus be referred back to the increased engagement of a pattern completion mechanism (Horner et

641 al., 2015). Second, the anterior CA3 involvement at closed-loop event retrieval cannot be explained

642 by mere recall success. Despite more holistic recollection at closed-loop events (i.e. higher retrieval

643 dependency and more nontarget reinstatement), accuracy levels in both event structure conditions

644 are similar. This rules out performance to be a driving factor in the functional activity pattern of

645 anterior CA3. Importantly, we observed CA3 activity in relation to the amount of holistic recollection

646 during the whole task, averaged across both event loop conditions (i.e. in relation to *overall* holistic

647 recollection). Thus, participants that generally engaged in more holistic recollection, showed more

648 CA3 activity when retrieving closed-loop events. In contrast, Horner and colleagues (2015) observed

649 that hippocampal involvement at retrieval of closed-loop events increased with the *difference* in

650 holistic recollection between closed and open-loop events. Small variations in our data may explain

651 the subtle differences in results. Even though we similarly observed higher nontarget reinstatement

652 at retrieval of closed-loop events (Figure 5), the difference to nontarget reinstatement at open-loop

653 events was smaller than in Horner et al. (2015). In our data, performance in both loop conditions was

654 higher and there was more holistic recollection in open-loop events (Figure 4; perhaps due to higher

655 performing participants inferring the missing associations), so that differences between closed- and

656 open-loop events were reduced.

657   While we leveraged the closed- versus open-loop contrast to examine specific hippocampal

658 involvement during holistic recollection via pattern completion, we do not claim that the

659 hippocampus is not involved in the recollection of open-loop associations. The hippocampus likely

660 mediates the associative memory required to answer the paired-associate questions regarding both

661 open- and closed-loop events. However, the open-loop events serve as a strict control condition, as

662 our data and previous literature indicate that there will be greater pattern completion for closed-

663 loop events, resulting in tighter dependency among elements and greater incidental reactivation of

664 nontarget elements (Horner et al., 2015; Horner & Burgess, 2014). Pattern completion is defined as a

665 computational mechanism on representational level (McClelland et al., 1995; Treves & Rolls, 1994).

666 We, however, took a univariate analysis approach here. Moreover, as we averaged across trials and

667 restricted our cortical reinstatement analysis to ROIs, we may not have captured the full variety in

668 the functional activity pattern at holistic recollection. Future studies need to verify pattern

669 completion mechanisms in the human CA3 on trial-specific level as well as directly on

670 representational level by multivariate approaches. The hippocampal effects need to be related to

28

671   cortical reinstatement beyond our restricted ROIs. In addition, future ultra-high resolution

672   neuroimaging studies should dissect the potential heterogeneity in the functional architecture along

673   the hippocampal axes. Such spatially and temporally more fine-grained analyses will have the

674   potential to show pattern completion effects in the human brain more explicitly.

675   To sum up, we acquired functional data in ultra-high resolution with 7 Tesla fMRI using the

676   established multi-element event paradigm by Horner and colleagues (2015). In accordance with

677   anatomical and animal research, our results yield first compelling empirical evidence for a functional

678   involvement of the human hippocampal subfield CA3 (but less pronounced in DG) in holistic

679   recollection via pattern completion. The current study contributes to our understanding of the

680   heterogeneous functional architecture within the human hippocampus.

681

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830

831

832   Figure Legends

833

834   *Figure 1.* Multi-element event paradigm (Horner et al., 2015). Participants learned 36 events that

835   consisted of multiple elements, with each element belonging to the location, people or object/animal

836   category. All events followed either a closed-loop structure [A] or an open-loop structure [B]. [C] At

837   encoding, events were learned in three blocks in a pairwise associative manner, one associative pair

838   at each block. [D] At retrieval, all three pairwise associations within each event were tested

839   bidirectionally. The 4-alternative forced choice recognition trial was followed by a confidence rating.

840

841   *Figure 2.* Example segmentation of hippocampal subfield dentate gyrus (DG, blue) and CA3 (yellow)

842   and coregistration from T2 to EPI space. The displayed images correspond to one participant. Manual

843   segmentation was performed on individual T2 images (Berron et al., 2017). Segmented masks were

844   then coregistered to the individual EPI space. Here, the coregistered masks are displayed on the

845   participant's mean EPI image, the lowest panel corresponds to the respective mean EPI. Crucial

846   hippocampal features for the segmentation (SLRM and the endfolial pathway on T2 images) are

847   indicated. Two corresponding slices in T2 and EPI space are shown from the hippocampal head (A)

848   and the hippocampal body (B). A sagittal view on the coregistration between an individual EPI and

849   the segmented hippocampal mask in T2 space (red outline) is presented in (C). EPI - echo-planar

850   image

851

852   *Figure 3*. Overview "hippocampal activity – nontarget reinstatement" analysis procedure. [A]

853   Calculation of participant-specific nontarget reinstatement values. At each retrieval trial one event

854   element serves as a cue and one is the target. The additional element remains incidental to the task -

855   that is the nontarget (i). From the previous "element-specific activity at retrieval" analysis, cortical

856   clusters have been identified that specifically relate to the respective element categories (i.e. PHC for

857   location, MPC for people, LOC for object) (ii). For each participant, beta values are extracted from the

858   respective cluster for the condition that the category's function at retrieval is to be a nontarget (iii).

859   Z-standardized beta values are averaged subsequently to obtain an overall nontarget reinstatement

860   value per participant. [B] Correlations between nontarget cortical reinstatement and hippocampal

861   activity. With a univariate first level GLM analysis, participant-specific contrast maps are obtained

862   that indicate the difference in hippocampal activity between the closed- and open-loop retrieval

863   condition. At group level that hippocampal activity pattern was correlated with the participant

864   specific nontarget reinstatement values. This yielded a statistical map, indicating hippocampal

865   activity at closed-loop retrieval that was scaled by the amount of nontarget reinstatement across

866   participants.

867

868   *Figure 4.* Behavioral dependency between multiple retrieval trials from closed- and open-loop

869   events. Observed dependency between trials from the same event was compared with estimated

870   dependency assuming fully independent and dependent models. Note that here depicted

871   dependency is calculated based on high confidence (level 3 – 4) versus collapsed low confidence

872   (level 1 – 2) and incorrect retrieval trials. Error bars ±1 SE.

873

874   *Figure 5.* Difference in cortical reinstatement between element functions (i.e. cue, target, nontarget)

875   [A] across loop conditions ("overall" cortical reinstatement) and [B] subtracting cortical

876   reinstatement at open-loop from closed-loop retrieval. [A] *denotes significant difference (p < .05),

877   [B] *denotes significant difference from zero (p < .05)

878

879   *Figure 6.* Functional hippocampal activity correlations at closed-loop retrieval with overall nontarget

880   cortical reinstatement. [A] Hippocampal cluster whose difference in activity between retrieval of

881   closed- versus open-loop events correlates with amount of non-target reinstatement across

882   participants (cluster size k = 35; *p(cluster)* = .028 (uncorr)). [B] Correlations between cue, target and

883   nontarget cortical reinstatement and the extracted beta values for closed- versus open-loop

884   retrievals from the identified hippocampal cluster, respectively. * denotes significant differences

885   between correlations ($p < .05$).

886

887   *Figure 7.* Functional activity correlations of subfield ROIs at closed-loop retrieval with overall

888   nontarget cortical reinstatement. Differences in activity between closed- and open-loop retrieval

889   were extracted as mean values from manually segmented hippocampal subfields CA3 and DG (right

890   anterior) and subsequently correlated with the amount of overall nontarget cortical reinstatement.

[A]

Object /Animal

Location   People

18 events in **closed-loop structure**

[B]

Object   Animal

Location   People

18 events in **open-loop structure**

[C]

Kitchen Hammer | Office Wallett — Kitchen Obama | Beckham Office — Obama Hammer | Lion Beckham

encoding

[D]

Obama

Office Kitchen
Lift Cinema

Obama

Confidence?
1 2 3 4

retrieval
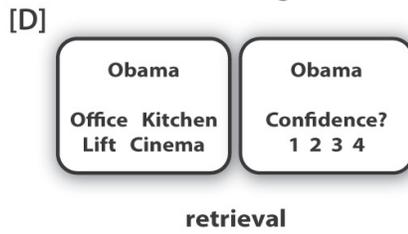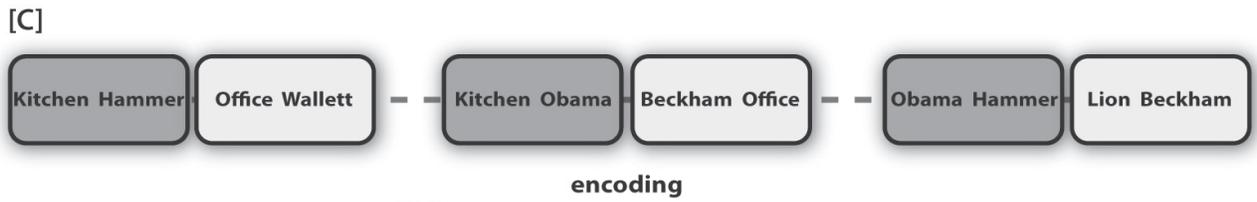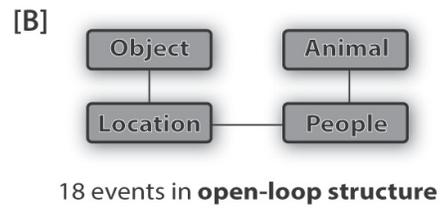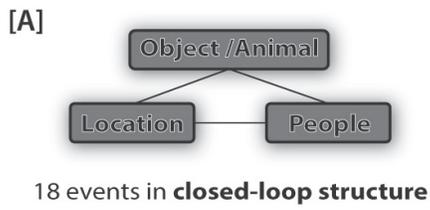
[A] **hippocampal head**　　　　　[B] **hippocampal body**

T2 image
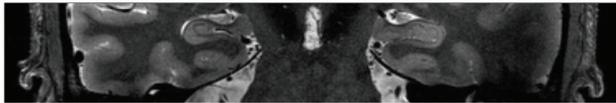
T2 image + segmented DG (blue) and CA3 (yellow)

endfolial pathway
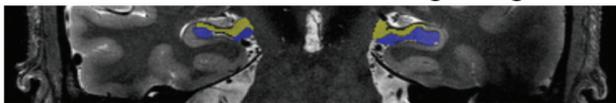
EPI image + coregistered DG (blue) and CA3 (yellow)

EPI image

SLRM

[C]

[A]

(i)   (ii)   (iii)

$\beta_{object\ nontarget}$

CUE

| Obama |
| Office   Kitchen |
| Lift   Cinema |

Hammer

NONTARGET

object

people

location

$\beta_{people\ nontarget}$

$\bar{X}_{\beta}$
nontarget
reinstatement

TARGET

$\beta_{location\ nontarget}$

element-specific cortical activity clusters
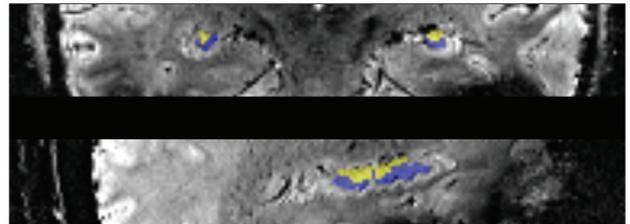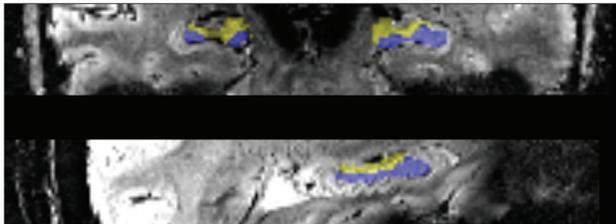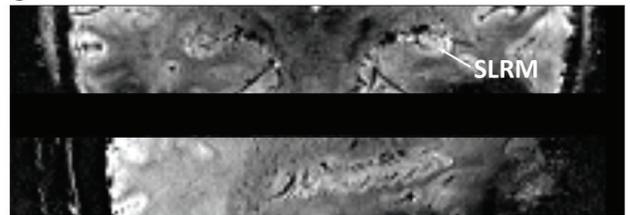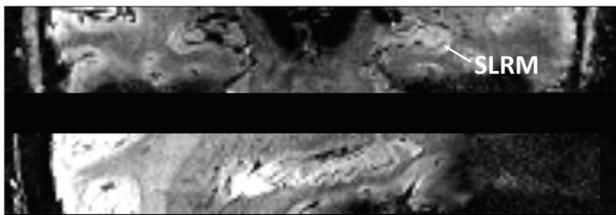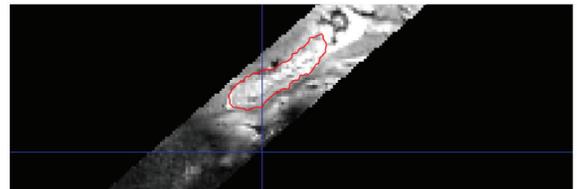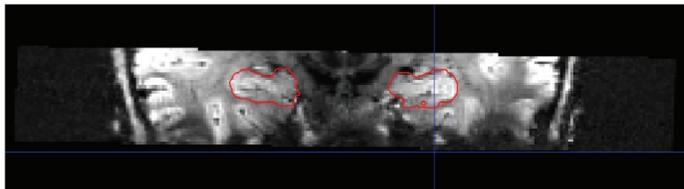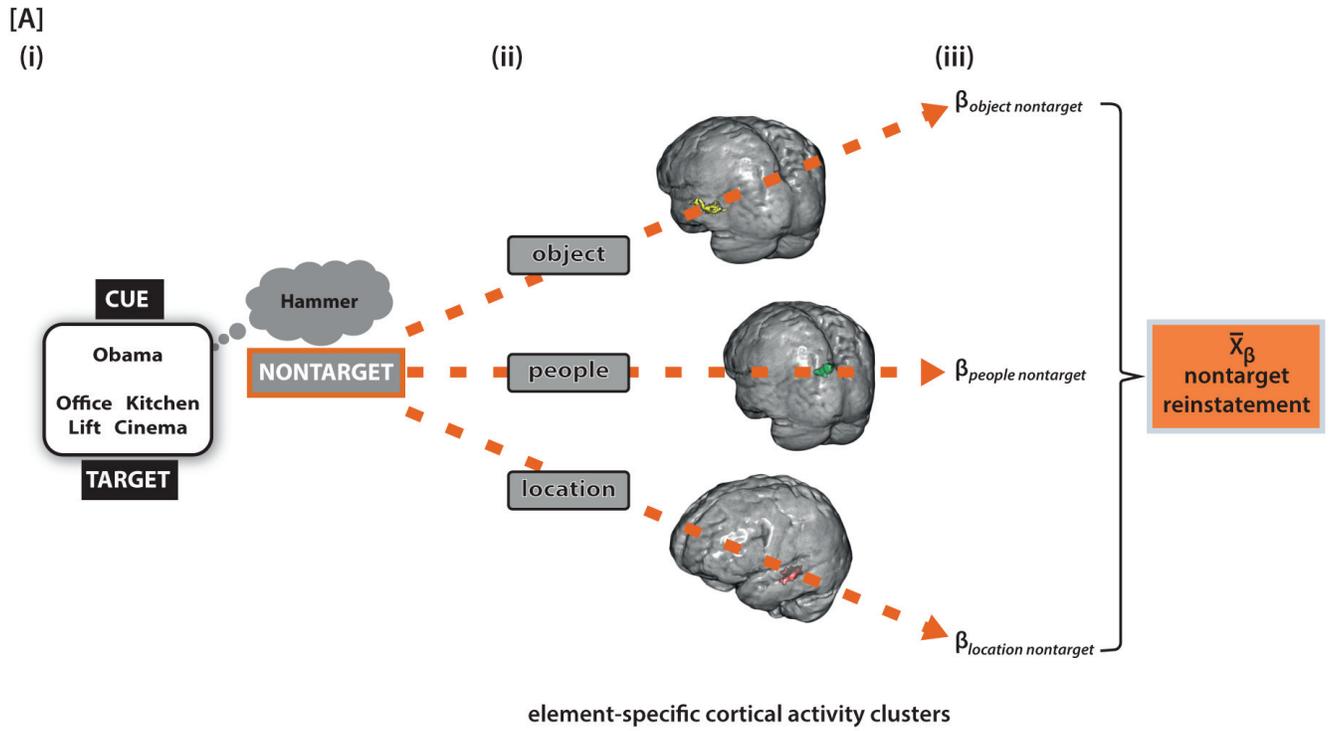
[B]

correlation between nontarget reinstatement and hippocampal activity at closed loop event retrieval

participant 4
participant 3
participant 2
participant 1

first level contrast maps
closed- versus open-loop event retrieval

nontarget reinstatement
per participant

[A]

overall cortical reinstatement
(across loop conditions)

*
*

cue   target   nontarget

[B]

cortical reinstatement
closed-loop versus open-loop

*

cue   target   nontarget

[A]

[B]

right anterior CA3 cluster (beta value)

CA3 right anterior

$R^2 = 0.16$
$p = 0.049$

DG right anterior

$R^2 = 0.04$
$p = 0.355$

nontarget cortical reinstatement

closed-loop versus open-loop (beta value)