THE UNIVERSITY *of* EDINBURGH

Edinburgh Research Explorer

Cortical pattern separation and item-specific memory encoding

OPEN ACCESS

Cortical pattern separation and item-specific memory encoding

Laura M. Pidgeon[a,b,*], Alexa M. Morcom[a]

[a] Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology, University of Edinburgh, UK
[b] Present address: School of Psychological Sciences and Health, University of Strathclyde, Glasgow, UK

Highlights:

- We examined cortical pattern separation and completion during episodic encoding
- Parametric similarity analyses assessed perceptual and conceptual dimensions
- Mnemonic discrimination of lures was associated with hippocampal encoding activity
- PFC and occipital pattern separation regions also predicted accurate recognition
- This is consistent with a role of cortical pattern separation in successful encoding

Abstract

Pattern separation and pattern completion are fundamental brain processes thought to be critical for episodic memory encoding and retrieval, and for discrimination between similar memories. These processes are best understood in the hippocampus, but are proposed to occur throughout the brain, in particular in sensory regions. Cortical, as well as hippocampal, pattern separation may therefore support formation of event-unique memory traces. Using fMRI, we investigated cortical pattern separation and pattern completion and their relationship to encoding activity predicting subsequent item-specific compared to gist memory. During scanning, participants viewed images of novel objects, repeated objects, and objects which were both perceptually and conceptually similar to previously presented images, while performing a size judgement task. In a later surprise recognition test, they judged whether test items were 'same' 'similar' or 'new' relative to studied items. Activity consistent with pattern separation – responses to similar items as if novel – was observed in bilateral occipito-temporal cortex. Activity consistent with pattern completion – responses to similar items as if repeated – was observed in left prefrontal cortex and hippocampus. Curve fitting analysis further revealed that graded responses to change in image conceptual and perceptual similarity in bilateral prefrontal and right parietal regions met specific computational predictions for pattern separation for one or both of these similarity dimensions. Functional overlap between encoding activity predicting

[*] **Correspondence to:** Laura M. Pidgeon, School of Psychological Sciences and Health, Graham Hills Building, 40 George Street, University of Strathclyde, Glasgow, UK, G1 1QE. Tel: +44141 5745292; email: Laura.Pidgeon@strath.ac.uk

subsequent item-specific recognition and pattern separation activity was also observed in left occipital cortex and bilateral inferior frontal cortex. The findings suggest that extrahippocampal regions including sensory and prefrontal cortex contribute to pattern separation and pattern completion of visual input, consistent with the proposal that cortical pattern separation contributes to formation of item-specific memory traces, facilitating accurate recognition memory.

1. Introduction

Sensory information from a changing environment is continuously processed by the brain, often resulting in substantial overlap between incoming representations and traces already stored in long-term memory. In order to avoid interference, incoming episodes must therefore be assigned unique neural representations. In the hippocampus, this is thought to be achieved by pattern separation - the orthogonalisation of incoming relative to existing representations. Conversely, overlapping input is used at retrieval as a cue to drive reinstatement of existing traces via pattern completion, increasing overlap between incoming and existing representations (Marr, 1971; McNaughton and Morris, 1987; O'Reilly and McClelland, 1994). Although pattern separation is by definition an encoding process, and pattern completion a retrieval process, either or both can be elicited by a single event, whether novel or previously encountered (Hunsaker and Kesner, 2013). Efficient pattern separation at encoding is thought to contribute to later *mnemonic discrimination* between events with similar representations, while false recognition of similar events can result from inefficient pattern separation or dominance of pattern completion at encoding (Sahay et al., 2011; Stark et al., 2013; Wilson et al., 2006). However the precise mechanisms by which pattern separation and completion at encoding contribute to memory outcomes remain unknown, and it remains to be established whether and how neocortex complements the central role of the hippocampus in these computations. The present study investigated cortical pattern separation and completion, and asked whether regions showing these responses were also engaged during encoding leading to later item-specific memory.

Within the hippocampus, computational, electrophysiological and lesion evidence has implicated the dentate gyrus (DG) in pattern separation, and subfields CA3 and CA1 in pattern separation or completion, depending on the degree of overlap between incoming and existing representations (Gilbert et al., 2001; Guzowski et al., 2004; Leutgeb et al., 2007; Rolls, 2007; Vazdarjanova and Guzowski, 2004). High-resolution functional magnetic resonance imaging (fMRI) evidence from humans is consistent with these findings. Typically, these studies have examined responses to novel images of common objects, repetitions of these images, and images of perceptually and conceptually similar objects. By examining neural responses to similar images within regions showing differential activity between novel and repeated images, it is assumed that equivalent activity between similar and novel items is consistent with pattern separation, i.e., similar images are processed as if novel, whereas equivalent activity to similar items and repetitions is consistent with

71   pattern completion, i.e., similar items are processed as if repeated. Examining regions showing

72   repetition suppression (Henson and Rugg, 2003), such investigations have reported activity consistent

73   with pattern separation in a region spanning DG/CA3, and pattern completion activity in CA1 and

74   elsewhere in the medial temporal lobe (MTL) (Bakker et al., 2008; Lacy et al., 2011). Although

75   pattern separation and completion investigations have focussed on the role of the hippocampus,

76   networks throughout the brain are thought to perform similar functions, including sensory cortex

77   (Aimone et al., 2011; Gilbert and Kesner, 2003). Rodent electrophysiological recordings have

78   demonstrated pattern separation of odour cues in the olfactory bulb, and pattern completion in

79   piriform cortex (Barnes et al., 2008; Wilson, 2009), but these functions in regions outside the MTL

80   have received little attention in studies in humans.

81   A number of fMR adaptation (fMRA) studies are also relevant to pattern separation and

82   completion processes. These have assessed the information represented in specific regions by

83   measuring stimulus-specific repetition suppression. Repetition suppression to exact repetitions but not

84   perceptually and conceptually similar images has been reported in visual cortical regions including

85   fusiform and lateral occipital cortex (LOC) (Chouinard et al., 2008; Koutstaal et al., 2001). Such

86   responses resemble pattern separation in that similar items elicit a response which is distinct from that

87   of repetitions. Repetition suppression to similar images which differ perceptually from previously

88   viewed items has also been observed in other occipito-temporal regions and in left inferior frontal

89   gyrus (LIFG) (Chouinard et al., 2008; Fairhall et al., 2011; Horner and Henson, 2011), resembling

90   pattern completion. Such findings together suggest that cortical regions contribute to the degree to

91   which visual inputs are coded as perceptually and semantically similar or distinct. However, evidence

92   for pattern separation or completion from these studies is incomplete. Some studies have reported

93   repetition suppression for repeated relative to both novel and similar items within the same anatomical

94   region without showing that these responses actually overlap (Bakker et al., 2008; Kumaran and

95   Maguire, 2009). Similarly, it has not yet been demonstrated that the regions showing repetition

96   suppression to similar items also show attenuated activity to repetitions, as expected for pattern

97   completion. One fMRA study however demonstrated occipito-temporal responses more clearly

98   consistent with pattern separation. Kim et al. (2009) reported release from repetition suppression in

99   bilateral LOC and fusiform in response to images which differed in shape but not basic-level concept

100   relative to previous images. LOC activity also did not differ between conceptually similar and

101   conceptually novel images equated in shape similarity with previously viewed images. Results were

102   interpreted as sensitivity of LOC to change in shape information, but can also be interpreted from a

103   pattern separation perspective, i.e., reduced activity for repetitions relative to both novel and similar

104   images, but activity for novel and similar items did not differ, providing the most direct evidence to

105   date of responses consistent with pattern separation in visual cortex.

106   Although the fMRA findings are suggestive of cortical pattern separation and completion, these

107   processes are computationally defined in terms of their responses to parametrically varied input

108 similarity (e.g., Treves and Rolls, 1992; Vazdarjanova and Guzowski, 2004). Therefore, examination

109 of neural responses to graded change in input, i.e., to stimuli of varying similarity relative to

110 previously presented items, can provide further support for their presence (Hunsaker and Kesner,

111 2013; Kumaran and Maguire, 2009). Pattern separation is defined as reduction in overlap of output

112 representations from a region relative to the degree of overlap of input representations received by the

113 region (Rolls, 1996; Treves and Rolls, 1992). The resulting changes in output in response to

114 increasing input similarity can therefore be approximated by a power function with decreasing slope,

115 i.e., a large difference in activity occurs between repeated and the most similar items (Fig. 1A; Motley

116 and Kirwan, 2012). In contrast, pattern completion *increases* the representational overlap at output

117 relative to input representations (O'Reilly and McClelland, 1994), approximated by a power function

118 with increasing slope, i.e., very slight differences in activity occur between repeated and similar items,

119 with only highly dissimilar items processed as if novel (Fig. 1; Vazdarjanova and Guzowski, 2004). In

120 regions showing repetition enhancement, the functions are the same but their direction is inverted

121 (Fig. 1B). A linear function represents the case where overlap is equal between input and output

122 representations, i.e., neither pattern separation nor completion occurs (Guzowski et al., 2004; Yassa

123 and Stark, 2011). 'Input' and 'output' here refer to neural representations, and in line with other

124 authors we approximate their similarity by that between items (Motley and Kirwan, 2012; Yassa et

125 al., 2011). fMRI responses consistent with these predictions have been demonstrated in hippocampus

126 in response to items of varied 'mnemonic similarity' (defining input similarity indirectly as the

127 probability of successful mnemonic discrimination in a separate sample; Lacy et al., 2011), or varied

128 viewing angle relative to previous images (Motley and Kirwan, 2012).

129 There has been little exploration in humans of the proposal that pattern separation at encoding

130 contributes to later mnemonic discrimination (Kirwan and Stark, 2007; Wilson et al., 2006). In

131 memory tasks incorporating similar lures at test as well as novel and studied items, successful

132 mnemonic discrimination entails correct rejection of lures (as 'similar' or 'new') as well as the ability

133 to recognise studied items, and lure false recognition reflects failed mnemonic discrimination.

134 Consistent with a role of pattern separation in mnemonic discrimination, in rats, lesions to DG,

135 strongly linked to pattern separation (e.g., Leutgeb et al., 2007), result in mnemonic discrimination

136 deficits (Goodrich-Hunsaker et al., 2008); and in humans, associations have been demonstrated

137 between both hyperactivation in CA3/DG and reduced perforant path integrity and poorer lure

138 discrimination performance (Kirwan et al., 2012; Yassa et al., 2010). Kirwan and Stark (2007)

139 reported that hippocampal (CA1, DG/CA3) but not other MTL regions showed encoding-related

140 activity which differentiated between later mnemonic discrimination outcomes (lure correct rejection,

141 lure false recognition, hits). They did not however examine the relation between this encoding activity

142 and pattern separation. Efficient pattern separation at encoding is thought also to facilitate recognition

143 of studied items as 'old' (Norman and O'Reilly, 2003; Yassa and Stark, 2011). Conversely, inefficient

144 pattern separation at encoding and/or emphasis of overlap between current and existing

145   < Figure 1 about here >

146

147 representations via pattern completion is assumed to contribute to later false recognition of similar

148 lures (Norman, 2010; Schacter et al., 1998; Yassa and Reagh, 2013).

149   Other theoretical accounts suggest that true and false recognition differ in terms of encoding

150 and retrieval of item-specific information. According to Fuzzy Trace Theory, gist traces are coarse,

151 acontextual representations of semantic information which are distinct from but encoded in parallel

152 with item-specific representations of precise surface form (Brainerd and Reyna, 1990; 2002). It is

153 suggested that false recognition of items overlapping in gist with studied items can result from

154 emphasis on gist processing at encoding, leading to increased strength of gist relative to item-specific

155 traces, and consequent reliance on gist at retrieval (Brainerd and Reyna, 2002). On this account, true

156 recognition of studied items can be supported by gist information alone, but is often associated with

157 intact item-specific memory in healthy, young adults (Gutchess and Schacter, 2012). In a recognition

158 test with an explicit requirement to respond 'similar' to lures, memory for gist in the absence of item-

159 specific memory may result in *partial recognition,* i.e., incorrectly judging studied items as 'similar'

160 (Garoff et al., 2005). Successful mnemonic discrimination of a similar lure from its previously studied

161 item is however thought to require intact item-specific memory as well as post-retrieval processing

162 (Brainerd et al., 2003). Several fMRI studies have shown differences in encoding activity according to

163 whether later memory is item-specific or gist-based. Activity in LIFG (Garoff et al., 2005; Kim and

164 Cabeza, 2007; Kubota et al., 2006) and left superior temporal gyrus (Baym and Gonsalves, 2010) has

165 been found to predict subsequent false recognition of images and visually presented words which are

166 semantically similar to studied items, relative to subsequent forgetting. The assumption that this

167 reflects semantic gist processing is consistent with behavioural studies showing that emphasis on

168 semantic processing at encoding contributes to greater likelihood of false memory (Koutstaal and

169 Schacter, 1997; Roediger and McDermott, 1995). However, contrasts of subsequent false recognition

170 with forgetting provide limited information about what is unique to encoding supporting mnemonic

171 discrimination. The same studies have found that encoding predicting true recognition engages visual

172 cortex, e.g. bilateral fusiform gyri, inferior temporal cortex and LOC (Baym and Gonsalves, 2010;

173 Garoff et al., 2005; Kim and Cabeza, 2007), suggesting additional perceptual processing may aid in

174 formation of item-specific memory. These regions associated with encoding predicting true and false

175 recognition are similar to those which in the fMRA studies discussed above were associated with

176 sensitivity and invariance to perceptual change, respectively (Fairhall et al., 2011; Kim et al., 2009;

177 Koutstaal et al., 2001). A small number of studies (Cheng and Rugg, 2010; Geng et al., 2007; Urbach

178 et al., 2005) have also reported differences in electroencephalographic event-related potentials during

179 encoding of words according to whether semantically similar lures are later mnemonically

180 discriminated or falsely recognised, consistent with suggestions that different encoding processes

181 contribute to these outcomes.

182   The present study had three main aims. First, we sought evidence for cortical activity consistent
183   with pattern separation and/or completion during incidental encoding of images of novel objects,
184   repetitions, and perceptually and conceptually similar objects (Bakker et al., 2008). We also assessed
185   whether neural responses to images of graded perceptual and conceptual similarity relative to
186   previously viewed images, defined by independent subjective ratings, met computational definitions
187   for pattern separation and completion within repetition sensitive regions. Second, we examined the
188   neural bases of encoding predicting recognition outcomes proposed to rely on item-specific memory
189   (mnemonic discrimination of lures), gist-based memory (partial recognition of studied items, false
190   recognition of lures) or both (true recognition). The recognition test employed studied, novel and lure
191   images and participants made 'same', 'similar' or 'new' judgements (Garoff et al., 2005; Koutstaal et
192   al., 1999). This task is thought to place greater demands on pattern separation than dichotomous
193   old/new recognition (Stark et al., 2013), and supports direct comparisons between successful and
194   unsuccessful lure mnemonic discrimination (Yassa et al., 2011). Finally, we assessed whether the
195   same regions engaged in pattern separation or completion were also associated with item-specific or
196   gist encoding.

197   Based on previous fMRA studies, it was predicted that bilateral inferior frontal cortex
198   (Koutstaal et al., 2001) and occipito-temporal regions including bilateral LOC and fusiform would
199   demonstrate pattern separation (Fairhall et al., 2011; Koutstaal et al., 2001), and would also be
200   engaged in item-specific encoding (Kim and Cabeza, 2007). Encoding predicting gist memory was
201   expected to engage left-lateralised regions associated with semantic processing, including fusiform,
202   inferior parietal lobe and LIFG (Badre and Wagner, 2007; Binder et al., 2009).

203

204   **2. Methods**

205   **2.1. Participants**

206   Twenty-six right-handed adults aged 18-26 years underwent fMRI scanning. Data from one
207   participant were lost due to data acquisition issues; a further five participants were excluded due to
208   chance performance on the recognition test. Results for pattern separation and pattern completion
209   analyses reflect data from the remaining 20 participants ($M = 21.9$ years; 10 female). For subsequent
210   memory analyses, seven further participants were excluded due to insufficient false recognition trials
211   (Section 2.7.1.). Subsequent memory analyses were therefore conducted on data from 13 participants
212   ($M = 21.8$ years; 6 female). Informed consent was obtained, and the protocol received ethical
213   approval. Subjective ratings of within-pair stimulus similarity were collected from a separate sample
214   (Section 2.4.).

215

216   **2.2. Materials**

Stimuli were pairs of images (photographs or drawings, 300 x 270 pixels) of common objects or animals (Koutstaal, 2006). Pairs comprised perceptually similar exemplars of the same basic-level conceptual category, e.g., cats, telephones. Study phase lists contained 280 images: 200 novel, 40 repetitions of previously presented images, and 40 images which were perceptually and conceptually similar to previously presented images. Test lists comprised 240 images: 80 studied ('same') items, 80 lures of studied items ('similar') and 80 novel ('new') items. Lures presented at test had not been presented at study. Of the studied items presented at test, 20 had been presented twice at study (as novel then as a repetition), and for 20 of the 80 lures presented at test, corresponding items had been presented twice at study. Allocation of images to conditions was counterbalanced across participants. For study and test phases, a unique pseudo-random order of presentation was generated for each participant, with the constraint that no more than six items from one condition were presented in sequence. At the start of the scanned study phase, four 'filler' images were presented, and excluded from analyses.

2.3. Task and procedure

Stimuli were presented in Cogent2000 v1.29 (www.fil.ion.ucl.ac.uk) in MATLAB v.7.12 (The MathWorks Inc., 2011). The task comprised a scanned study phase and a subsequent recognition test, illustrated in Fig. 2. Stimuli were displayed through MRI-compatible Nordic Neurolab goggles (www.nordicneurolab.com) at an effective viewing distance of 1 m, and vision was corrected to normal if required. Images subtended approximately 10 degrees of visual angle. Earplugs were employed to reduce scanner noise, and head motion was minimised using foam pads. During the study phase, participants judged whether each depicted item would fit in a shoebox, responding 'yes' or 'no' via button presses on hand-held fibre-optic response pads. Images were presented centrally against a white background for 2200 ms, followed by a black fixation cross for 300 ms, then a red fixation cross for 300 ms (stimulus onset asynchrony (SOA) = 2800 ms). Novel images were separated from corresponding repetitions or similar images by 30 - 60 trials. Participants also viewed 40 fixation-only 'null' trials, in which the black fixation cross remained onscreen for the duration of one SOA.

Twenty-four hours after the study phase, participants completed a recognition test. Participants judged whether images presented were 'same', 'similar', or 'new' relative to studied items, or gave a 'guess' response. Responses were made via key presses. Images were presented for 3000 ms with a 1000 ms inter-trial interval (black fixation cross 700 ms, red fixation cross 300 ms; SOA = 4000 ms). Assignment of keys to responses was counterbalanced across participants. Practice sessions were conducted prior to study and test phases.

< Figure 2 about here>

2.4. Similarity ratings

Subjective similarity ratings were collected from a separate sample ($N = 23$; 18 – 25 years). The pairs of images employed in the main experiment were presented in sequence, with a unique pseudorandom order of presentation generated for each participant. Twelve participants rated the perceptual similarity of items within each pair from 1 (highly similar) to 5 (highly distinctive), and 11 rated intra-pair conceptual similarity on the same scale. Participants were asked to base perceptual similarity judgements on visual features such as shape or colour, and to base conceptual similarity judgements on how well the images corresponded to the same *kind* of object, i.e., two mountain bikes would be judged as conceptually similar, whereas a collie and bulldog, although both belonging to the basic-level category 'dog' should be rated less conceptually similar (Konkle et al., 2010). Image pairs were presented until 800 ms after a response was made, up to a maximum presentation time of 6000 ms. Between trials, a black fixation cross was presented for 1000 ms.

2.5. fMRI data acquisition

Images were acquired with a 1.5T Signa Horizon HDX MRI scanner operating under a research collaboration with GE Medical Systems (Milwaukee, USA). T2*-weighted functional images were acquired in a single session using a BOLD-EPI sequence (TR = 2200 ms, TE = 40 ms). Functional data consisted of 435 volumes, each comprising 30 slices (interleaved acquisition; 64 x 64 matrix; 4 mm x 4 mm x 4 mm). The first 4 volumes were discarded to account for T1 equilibration. Following functional scanning, T1-weighted structural images were obtained (fov = 24 cm; flip angle 8°, 256 x 256 matrix, 1mm x 1mm x 1.3 mm voxels).

2.6. Image preprocessing

MRI preprocessing and analysis were conducted in SPM8 (Wellcome Department of Cognitive Neurology, London, UK) in MATLAB v.7.5 (The MathWorks Inc., 2007). Scans with slices showing average signal of greater than 7 standard deviations (*SD*) from the session mean were visually checked, and where artefacts were present scans were replaced with the average of the two adjacent scans (Foo et al., 1994) then modelled as confounds in the first level design matrix (see Section 2.7.1.). Functional images were corrected for temporal differences in slice acquisition using sinc interpolation in time, and spatially realigned to the mean EPI image using B-spline interpolation. For whole-brain analyses, spatial normalisation used the 'new segment' protocol in SPM8 (Ashburner and Friston, 2005): participants' structural scans were coregistered to their mean EPI image, then segmented into 6 tissue classes. Resulting parameters were applied to reslice the EPI images to 3 x 3 x 3 mm voxels in Montreal Neurological Institute (MNI) space. Finally, for the principal analyses the data were spatially smoothed with an 8 x 8 x 8 mm full-width half maximum Gaussian kernel.

2.7. fMRI data analysis

2.7.1. First and second level models and statistical thresholding

At the first level, vectors of onset times for each event type of interest for each participant were convolved with the canonical haemodynamic response function (HRF) and temporal derivative basis functions in a general linear model (GLM). Hypothesis testing involved construction of 5 separate first level models. Model i) implemented the overall pattern separation/completion analysis, and ii)-iv) the input similarity analyses. For the similarity analyses, model ii) identified repetition sensitive regions, then iii) modelled perceptual similarity and iv) conceptual similarity. Finally, v) modelled subsequent memory effects.

For the overall pattern separation and completion model (i), event types of interest were novel, repeated and similar items. Unlike previous fMRI studies, we defined pattern separation and completion within regions showing repetition enhancement as well as suppression. A difference in activity between novel and repeated items is necessary to reveal the relative responses to similar items, but both directions of repetition effect are consistent with computational definitions for pattern separation and completion. In ii), to define repetition sensitive regions the event types of interest were the novel and repeated items presented at study. For each participant, half of the novel items for which repeated or similar items were later presented, and half of the repeated items (40 and 20, respectively) were randomly selected to identify the repetition sensitive regions, and the remaining half were used for the similarity analyses iii) and iv). In ii), the 120 novel non-repeated items were also included to maximise sensitivity. For similarity analyses, stimulus pairs were divided into tertiles based on their average intra-pair perceptual (ii) and conceptual (iii) similarity ratings. Event types of interest were: novel items for which similar or repeated items were later presented; repetitions; similar items of high (S1); medium (S2); and low (S3) similarity; and null events. The novel and repeated items consisted of the half of the novel and repeated items (40 and 20) not included in the mode used to select repetition sensitive regions (ii). For model iii), for each class of similar item (S1, S2, S3), a continuous measure of perceptual similarity was included as a parametric modulator, convolved with the canonical HRF. Similarly, for model iv), continuous measures of conceptual similarity were included as parametric modulators for each of the similar conditions (S1, S2, S3). For models iii) and iv), novel items which were not subsequently repeated (either as similar items or repetitions) served as a non-fixation implicit baseline, following Motley and Kirwan (2012). For the subsequent memory model (v), encoding trials were sorted according to the response condition of corresponding studied/lure items at test. Event types of interest were hits to studied items ('same'|studied), partial recognition of studied items ('similar'|studied); lure false recognition ('same'|lure); lure correct rejection ('similar'|lure); and 'forgetting'. For the latter event type, misses to both studied items and

323　lures ('new'|studied; 'new'|lure) were collapsed into a single category. Participants with fewer than 10

324　trials in any condition of interest were excluded from analyses.

325　　For all models, the first two images presented during scanning and, for the subsequent memory

326　model, trials receiving no response, were modelled as events of no interest. Regressors comprising a

327　'1' in a column of zeroes representing removed scans were also included in the GLM as confounds,

328　along with 12 motion parameters comprising the six rigid-body transformation outputs of the

329　realignment stage, and the differences between these six parameters and the corresponding parameters

330　of the previous scan (Friston et al., 1996). The time series was high-pass filtered using a cut-off of 128

331　s, and parameter estimates were computed using the weighted least squares model fitted to the data

332　after prewhitening using an AR(1) plus white noise model (Friston et al., 2002).

333　　For models i), ii) and v), fMRI data were analysed using a two stage summary statistic mixed-

334　effects procedure (Penny and Holmes, 2006) (for iii and iv, group analyses were conducted on beta

335　values extracted from first level models, Section 3.2.2.1.). *T*-contrasts for each event type (e.g., for

336　pattern separation: novel, repetition, similar) against the implicit baseline were computed at the

337　individual subject level and entered into one-way within-subjects analyses of variance (ANOVAs) at

338　the group level, which modelled average subject effects and treated participants as random effects.

339　GLMs were estimated using weighted least squares to account for non-sphericity (Friston et al.,

340　2002). Main contrasts of interest employed one-tailed *t*-tests, producing statistical parametric maps of

341　*t*-statistics at each voxel. Images for exclusive masking were computed using bidirectional *F*-tests.

342　Correction for multiple comparisons employed AlphaSim's Monte Carlo permutation-based cluster

343　threshold (Analysis for Functional NeuroImaging, afni.nimh.nih.gov; Cox, 1996). For a family-wise

344　error (FWE) rate of $p < .05$, given a cluster-defining voxel threshold of $p < .01$, the cluster threshold

345　was 67 contiguous voxels for whole-brain contrasts. Exclusive masks were applied at an uncorrected

346　threshold of $p < .05$, to discount voxels from the resulting masked contrasts which showed any hint of

347　the relevant masked effect. Results reported are for the canonical HRF.

348

349　**2.7.2. Cortical region of interest (ROI) analyses**

350　　Pattern separation and subsequent memory effects were also examined in several *a priori* ROIs,

351　listed in Table 1 along with a summary of the results of the analyses (see Section 3.2.). For each ROI,

352　average beta values from first level models were extracted for event types of interest within spheres of

353　5 mm radius (3 mm in MTL) centred on peak coordinates from previous relevant studies. Differences

354　in extracted beta values between events of interest were analysed using *t*-tests and ANOVA.

355
356
357
358　　　　　　　　　　　　　　　< TABLE 1 about here >
359

2.7.3. Hippocampal voxel-wise ROI analysis

In line with previous fMRI studies of pattern separation and pattern completion, targeted analyses were also conducted within the hippocampus using unsmoothed EPI data. To ensure optimal localisation and signal detection, the ROI-AL method of cross-participant alignment was used (Stark and Okado, 2003). Given the limited spatial resolution, both hippocampi together were treated as a single ROI. T1 structural scans were first normalised to MNI space in SPM8 using affine transforms, before hippocampal manual segmentation in ITK-SNAP (Boccardi et al., 2011; Yushkevich et al., 2006). Resulting segmentations were aligned using the Diffeomorphic Demons algorithm (Vercauteren et al., 2007) in MedINRIA (v1.8.0, ASCLEPIOS Research Team, France) to a hippocampal mask derived from manual segmentation of the T1 canonical brain. Segmentations were then realigned to a template derived from the mean of the post-aligned ROIs from the previous step. The displacement fields generated were applied to participants' preprocessed EPI time series, and first and second level models re-estimated (Section 2.7.1.). Voxel-wise analyses were conducted within the group hippocampal mask. For a FWE of $p < .05$ given a cluster-defining voxel threshold of $p < .01$, a cluster threshold of 3 voxels was determined using AlphaSim.

2.7.4. Functional overlap

We tested for joint significance of the conjunction of each pattern separation or completion contrast with each item-specific or gist encoding contrast which revealed significant findings. A conjoint voxel threshold was applied following inclusive masking of each encoding contrast with the relevant pattern separation/completion contrast. With the individual contrasts thresholded at the original significance level of $p < 0.01$, the conjoint uncorrected voxel significance level was $p < .001$ according to Fisher's formula (Fisher, 1950; Lazar et al., 2002). Using AlphaSim, the cluster threshold for FWE correction at $p < .05$ given this conjoint voxel significance level was 20 contiguous voxels.

3. Results

3.1. Behavioural results

3.1.1. Study phase

One-way ANOVA examining mean reaction time (RT) at study showed that responses on the size judgement task were faster to repetitions (830 ms) and similar items (863 ms) compared to novel items (953 ms; $F(2,38) = 38.4$; $t(19) = 8.06$; $t(19) = 6.52$; all $p < .001$). No differences were observed in RT at study according to memory response at test ($F < 1$). As the size judgement task contained a subjective element, accuracy was not assessed.

394

3.1.2. Test phase

Analyses of test phase memory accuracy and RTs were conducted on data from the 13 participants included in subsequent memory analyses. RT at test differed according to the Condition of items (studied, repetition, lure; $F(2,24) = 14.31$, $p < .001$) and the Response given ('same', 'similar', 'new'; $F(2,24) = 7.24$, $p = .003$). A Condition x Response interaction ($F(4,48) = 7.15$, $p < .001$) was followed up via t-tests contrasting correct with incorrect responses separately for each Condition. For studied items, correct 'same' responses were faster than incorrect responses ('similar': $t(12) = 4.72$, $p = .001$; 'new': $t(12) = 2.18$, $p = .05$). Novel items were correctly identified as 'new' faster than they were incorrectly judged 'same' or 'similar' ($t(12) = 2.35$, $p = .037$; $t(12) = 3.21$, $p = .007$). Participants were slower to correctly reject lures than to falsely recognise lures as 'same' ($t(12) = 2.25$, $p = .04$), and no difference in RT was observed between correct 'similar' and incorrect 'new' responses to lures ($t(12) = 1.96$, $p = .07$).

Proportions of responses associated with each Condition (studied, lure, novel) at test were computed for the 13 participants included in subsequent memory analyses (see Fig. 3). Three one-way ANOVAs examined effects of Condition (studied, lure, novel) separately for each Response ('same', 'similar', 'new'). Effects of Condition were present for each Response ('same': $F(2,24) = 234.83$, $p < .001$; 'similar': $F(2,24) = 27.22$, $p < .001$; 'new': $F(1.2,14.7) = 71.0$, $p < .001$). *Post hoc* tests for each Response type (adjusted $\alpha = .017$) revealed that correct 'same' responses to studied items were more frequent than false recognition of lures or novel items ($t(12) = 15.17$; $t(12) = 16.82$; ps $< .001$), and lures were falsely recognised more often than novel items ($t(12) = 9.48$, $p < .001$). 'Similar' responses were assigned to lures more often than studied or novel items ($t(12) = 8.13$; $t(12) = 5.25$; ps $< .001$), but there was no difference in the proportions of studied and novel items judged 'similar' ($t(12) = .58$, $p = .58$). Novel items were judged 'new' more often than studied items or lures ($t(12) = 8.85$; $t(12) = 8.02$; ps $< .001$), and studied items received fewer 'new' responses than lures ($t(12) = 7.02$, $p < .001$).

< Figure 3 about here >

3.1.3. Similarity ratings

The average perceptual similarity rating of image pairs was 2.89 ($SD = .68$, range 1.33 - 4.58) and the average intra-pair conceptual rating was 3.01 ($SD = .63$, range 1.64 - 4.45). Conceptual and perceptual ratings were positively correlated across items ($r = .64$, n = 280, $p < .001$).

3.2. fMRI results

3.2.1. Pattern separation and pattern completion

3.2.1.1. Analysis strategy

430   To assess pattern separation, we searched for regions in which average activity elicited by
431   novel and similar items was greater than activity for repetitions (repetition < similar = novel), using a
432   one-tailed *t*-contrast at the group-level. To discount regions showing any hint of differential activity
433   between novel and similar items, the resulting SPM was exclusively masked with the bidirectional *F*-
434   contrast of novel vs. similar (Section 2.7.1.). To detect pattern separation activity in regions showing
435   greater activity for repetitions than novel items, a 'reverse' pattern separation contrast was computed
436   (repetition > similar = novel), again exclusively masked with the *F*-contrast of novel vs. similar. For
437   pattern completion, *t*-contrasts located regions in which activity elicited by novel items was greater
438   than that for both similar items and repetitions (repetition = similar < novel), exclusively masked with
439   the *F*-contrast of similar vs. repeated items. A 'reverse' pattern completion contrast also examined
440   regions showing increased activity to similar and repeated relative to novel items (repetition = similar
441   > novel).
442

443 *3.2.1.2. Findings*

444   Regions showing suprathreshold pattern separation and completion-consistent activity in the
445   whole brain analysis are summarised in Table 2 and selected regions are illustrated in Fig. 4 (pattern
446   separation) and Fig. 5 (pattern completion). Pattern separation (repetition < similar = novel) activity
447   was observed in bilateral PFC and occipito-temporal regions including a lateral prefrontal region
448   encompassing LIFG (BA 46) and left middle frontal gyrus (LMFG; BA 9), and right inferior frontal
449   gyrus (RIFG; BA 9), right inferior temporal cortex and left middle temporal gyrus. Reverse pattern
450   separation activity (repetition > similar = novel) was observed in right inferior parietal cortex. Pattern
451   completion activity (repetition = similar < novel) was revealed in a region of LIFG (BA 46/47) which
452   overlapped but was slightly more anterior to that revealed in pattern separation contrasts. The
453   'reverse' pattern completion contrast (repetition = similar > novel) revealed activity in left superior
454   frontal and left supramarginal gyri, and right precuneus.

455   The *a priori* ROI analyses (Table 1) revealed activity consistent with pattern separation in right
456   fusiform, bilateral middle occipital cortex, and posterior LIFG (BA 44). Voxel-wise ROI analysis in
457   hippocampus showed pattern completion activity in a left anterior region (Table 3).

458

459   < TABLE 2 about here>

460

461   < FIGURE 4 about here >

462

463   < FIGURE 5 about here>

464

465   <TABLE 3 about here >

466

467   **3.2.2. Input similarity**

468   *3.2.2.1. Analysis strategy*

469   To ensure independence of input similarity analyses from the ROI selection procedure,
470   repetition sensitive regions were first identified by conducting unidirectional *t*-contrasts of novel >
471   repeated, and repeated > novel using half of the items in each of these conditions (Section 2.7.1. for
472   model and thresholding; Table 4 for results). Voxel-wise ROI analysis in the hippocampus did not
473   reveal any repetition sensitive regions which survived thresholding, so model fit was examined in
474   cortical repetition sensitive regions (Table 4) and *a priori* ROIs (Table 1) only. Input similarity
475   analyses were conducted using the remaining half of the novel and repeated items within ROIs
476   centred on the peak voxels of all regions which showed significant differences between novel and
477   repeated items, and for the *a priori* ROIs for which pattern separation was supported in whole-brain
478   analyses (Section 3.2.1.2.). Next, beta values extracted from first level models for each ROI were
479   averaged across participants for each trial type – repetitions, high (S1), medium (S2), and low (S3)
480   similarity items, and first presentations of novel items. Using the Curve Fitting Toolbox (v3.4) in
481   MATLAB (v8.2), linear ($f(x) = ax + b$) and power functions ($f(x) = ax^b + c$) were fitted to the data for
482   each ROI, with each data point weighted by the inverse of the square of the standard error (Machluf,
483   2008). Power functions with decreasing slope are defined as functions where b (the exponent) < 0,
484   and increasing slope power functions where $b > 1$ (Motley & Kirwan, 2012). The least squares
485   analogue of Akaike's Information Criterion, including correction for small sample size (AIC_c) was
486   calculated using: $AIC_c = n\log(SSE/n) + 2K + (2K(K+1))/(n-K-1)$, where n is the sample size, SSE is
487   the sum of squared error, and K is the number of model parameters, including the error term
488   (Burnham and Anderson, 1998). For each similarity measure, comparative fit of each linear and
489   power model was assessed via AIC_c, adopting the criterion that a difference in AIC_c of greater than 4
490   corresponds to significant evidence of a difference in model fit (Burnham and Anderson, 1998), with
491   better fit for the model with the lower AIC_c value. To avoid formal comparison of very poor fitting
492   models, model fit was compared using AIC_c only where adjusted $R^2 > 0$ (indicating the model
493   provides better fit than a horizontal line) for one or both models.
494   For five out of six repetition sensitive regions, the peak voxel coordinates fell within a pattern
495   separation or completion cluster revealed in the whole-brain contrasts (Section 3.2.1.2.). Findings of
496   the curve fitting analysis were therefore interpreted in light of this overlap, to determine whether fitted
497   curves were consistent with the overall analysis. The predicted function for pattern separation in
498   regions showing repetition suppression (including *a priori* ROIs) was a power function with

499   decreasing slope (above the diagonal in Fig. 1A) for responses to repetitions, items of high, medium

500   and low similarity, and novel items, The predicted function for pattern completion was a power

501   function with increasing slope. Using a stricter operationalisation of pattern completion than Motley

502   and Kirwan (2012), who also interpreted linear functions as evidence of pattern completion, we

503   classified a linear function as consistent with neither pattern separation nor completion (see

504   Introduction). In regions showing repetition enhancement, the direction of response functions

505   consistent with pattern separation and completion was reversed: pattern separation is expected to

506   approximate the decreasing slope power function below the diagonal in Fig. 1B, and pattern

507   completion the increasing slope power function above the diagonal.

508
509   <TABLE 4 about here>

510   *3.2.2.2. Findings*

511   Repetition sensitive regions are summarised in Table 4. Model fit is summarised in Table 5,

512   and full model parameters are listed in Supplementary Table S1. Best fitting curves for ROIs showing

513   model fit consistent with pattern separation are depicted in Fig. 6. The RIFG cluster overlapped with

514   an RIFG cluster revealed in the whole-brain pattern separation contrast (repetition < similar = novel)

515   and showed decreasing slope power functions for both conceptual and perceptual similarity,

516   consistent with pattern separation. AIC_c differences between the power and linear models were 13.33

517   and 14.46 for conceptual and perceptual similarity, respectively, and for both similarity measures,

518   linear models showed very poor fit (adjusted $R^2 < 0$), suggesting better fit for the power function. The

519   right superior temporal gyrus cluster overlapped with a right inferior parietal reverse pattern

520   separation cluster (repetition > similar = novel) but did not show sufficiently reduced AIC_c for the

521   best fitting decreasing slope power function for conceptual similarity relative to the linear function

522   (AIC_c difference = 1.56). However, the right supramarginal gyrus subpeak of this cluster was closer to

523   the peak of the overlapping right inferior parietal cluster (4.2 vs.14.7 mm; see Table 4) and showed

524   better fit for the decreasing slope power model for conceptual similarity, consistent with pattern

525   separation (AIC_c difference = 19.41).

526   Among the *a priori* ROIs, posterior LIFG showed the predicted power function with decreasing

527   slope for conceptual similarity, indicative of pattern separation and consistent with the overall

528   analysis (AIC_c difference =8.59). Contrary to predictions however, the right middle occipital (RMO)

529   ROI showed best fitting *increasing* slope power functions for both conceptual and perceptual

530   similarity (AIC_c differences = 29.42 and 18.31). For all other ROIs, including a left anterior cingulate

531   region which did not overlap with pattern separation or completion regions, support for the predicted

532   pattern separation or completion function was not found.

533
534   < TABLE 5 about here >

535   < FIGURE 6 about here >

536

537

3.2.3. Subsequent memory

3.2.3.1. Analysis strategy

Encoding trials were sorted according to responses in the subsequent recognition test (see Fig. 3). Subsequent hits to studied items and subsequent correct rejection of lures were classified as item-specific memory, while subsequent partial recognition of studied items as 'similar' and subsequent false recognition of lures as 'same' were classified as gist memory (Garoff et al., 2005). Misses ('new' responses) of studied items and lures comprised the subsequent forgetting category. Hits versus partial recognition of studied items, and correct rejection versus false recognition of lures were analysed as two distinct subsequent memory effects, one relating to encoding supporting recognition of studied items, the other to encoding supporting mnemonic discrimination of lures (Cheng and Rugg, 2010). To examine encoding predicting gist memory, we used unidirectional *t*-contrasts to identify activity increases for subsequent partial recognition relative to subsequent hits; and for subsequent false recognition relative to subsequent lure correct rejection. As both partial and false recognition have been proposed to reflect gist memory (Garoff et al., 2005), to maximise trials available for gist contrasts and to allow comparison with the results of Garoff et al. (2005), additional contrasts also collapsed subsequent partial and false recognition into a single 'gist memory' category, and compared this separately with subsequent hits and subsequent correct rejection. The reverse contrasts were also computed (subsequent hits > subsequent partial recognition; subsequent correct rejection > subsequent false recognition, and each item-specific memory outcome > subsequent gist memory). Finally, each response category was also contrasted with subsequent forgetting.

3.2.3.2. Findings

Results of the subsequent memory analyses are summarised in Table 6. Encoding of items attracting subsequent hits, when compared with subsequent gist memory (partial recognition of studied items and false recognition of lures) elicited greater activity in right superior temporal gyrus, posterior LIFG, and left middle occipital gyrus. The contrast of subsequent hits vs. subsequent partial recognition revealed activity in right precuneus and left middle occipital gyrus. Encoding predicting lure correct rejection compared to lure false recognition elicited greater activity in posterior cingulate. Encoding predicting subsequent gist memory, when contrasted with encoding predicting subsequent lure correct rejection, revealed activity in left inferior parietal lobe.

569   < TABLE 6 about here >

570

571   The voxel-wise analysis in the hippocampus showed that activity in right posterior and left
572   anterior regions predicted subsequent correct rejection of lures relative to subsequent gist memory
573   (Table 3). Activity in a left posterior region was also greater for encoding of items for which lures
574   were subsequently falsely recognised compared to items for which lures were correctly rejected.

575

576   **3.2.4. Overlap between pattern separation/completion and item-specific/gist encoding**

577   *3.2.4.1. Analysis strategy*

578   Functional overlap between pattern separation or pattern completion and mnemonic encoding
579   was assessed by searching for regions showing conjoint activity between significant contrasts
580   employed in pattern separation and subsequent memory contrasts (see Sections 2.7.1., 3.2.1.1. &
581   3.2.3.1. for masking and thresholding procedures) for the 13 participants included in both analyses.

582

583   *3.2.4.2. Findings*

584   The conjoint analysis revealed significant functional overlap between regions engaged in
585   pattern separation and encoding predicting hits to studied items (Table 7 & Fig. 7). Bilateral inferior
586   frontal and left middle occipital regions showed both pattern separation (repetition < similar = novel)
587   and greater activity for subsequent hits than subsequent gist memory. Overlap was also observed
588   between pattern separation activity and encoding activity predicting subsequent hits relative to
589   subsequent partial recognition in left occipital and right inferior frontal cortex. No significant
590   functional overlap was observed between pattern separation and gist encoding, or between pattern
591   completion and either item-specific or gist encoding.

592

593   < TABLE 7 about here >
594   < FIGURE 7 about here >

595

596

597   **4. Discussion**

598   This is the first study to investigate cortical pattern separation and completion of visual object
599   representations in humans. We found neural activity consistent with pattern separation in occipito-
600   temporal cortex and bilateral lateral PFC, and pattern completion in left anterior PFC and right
601   precuneus. In bilateral lateral PFC, and right parietal regions, responses to parametrically varied
602   conceptual and perceptual input similarity provided further evidence for pattern separation. The data

603   are in line with computational predictions (Treves and Rolls, 1992; Vazdarjanova and Guzowski,
604   2004) and with findings of pattern separation and completion computations in sensory cortex in
605   rodents (Aimone et al., 2011; Barnes et al., 2008). Bilateral prefrontal and left occipital cortex regions
606   showing pattern separation activity were also engaged during encoding predicting subsequent true
607   recognition, consistent with suggestions that cortical pattern separation contributes to successful item-
608   specific encoding. Contrary to predictions, we did not detect overlap between pattern separation
609   activity and encoding activity associated with later mnemonic discrimination of lures, although
610   activity in the hippocampus did predict accurate lure rejection, in line with previous findings (e.g.,
611   Kirwan & Stark, 2007). The data are consistent with the view that cortical pattern separation at
612   encoding contributes to successful item-specific memory, but that further processes, such as encoding
613   of gist and item-specific information, contribute to later mnemonic outcomes.
614

4.1. Behavioural findings

616   Reaction time data did not reveal any evidence that later recognition outcomes were due to
617   differences in duration of processing at study. Faster RTs at study to both repeated and similar items
618   are consistent with priming of similar items based on overlapping perceptual or conceptual features
619   (Stenberg et al., 2009). Performance on the 'same/similar/new' recognition test was similar to that in
620   previous reports (Garoff et al., 2005; Stark et al., 2013; Toner et al., 2009) with participants most
621   often correctly classifying studied, lure and novel images as 'same', 'similar' and 'new', respectively.
622   Proportions of 'similar' responses to each item type were lower than in Garoff et al.'s (2005) earlier
623   study which employed the same retention interval and largely the same stimulus set. This may be
624   explained by the fact that in Garoff et al.'s (2005) study, a higher proportion of test items were lures
625   (2/5) compared to the current study (1/3), which may have led to greater bias to respond 'similar' in
626   the original study. This may also be why responses here but not in the previous study were also less
627   accurate for lures than for studied and novel items. The pattern observed here is consistent with
628   previous findings of reduced performance for lures (e.g., Stark et al., 2013; Toner et al., 2009), and
629   with claims that lure discrimination places greater demands on pattern separation (Kirwan and Stark,
630   2007; Yassa et al., 2011) and/or post-retrieval processing (Brainerd et al., 2003; Morcom, 2015) and
631   is therefore associated with reduced accuracy.
632

4.2. Pattern separation and pattern completion

634   As predicted, contrasts of study phase activity elicited by novel, repeated and all similar items
635   revealed evidence of pattern separation in bilateral occipito-temporal cortex in both *a priori* and
636   whole-brain analyses. This is consistent with neurophysiological evidence of orthogonalisation of
637   input in sensory cortex (Barnes et al., 2008; Wilson, 2009). These findings extend those of fMRA

638 studies reporting sensitivity of visual regions to subtle perceptual change in images (Chouinard et al.,
639 2008; Kim et al., 2009; Koutstaal et al., 2001), by identifying occipito-temporal clusters of activity
640 that show differential activity between repetitions and both novel and similar items, with no hint of
641 activity differences between novel and similar items. Curve fitting analysis did not however provide
642 additional support for true computational pattern separation in occipito-temporal regions.

643 We also observed activity consistent with pattern separation in bilateral, mainly posterior and
644 inferior, regions of lateral frontal cortex. In bilateral inferior frontal and right parietal areas,
645 converging evidence from the overall analyses and from curve fitting supported pattern separation,
646 indicative of sensitivity to item novelty despite overlapping representations. The prefrontal regions
647 have been linked to cognitive control functions including selection among competing memory
648 representations (Badre and Wagner, 2007; Dudukovic and Wagner, 2007), and goal-related attentional
649 modulation of sensory signals in extrastriate visual regions (Zanto et al., 2011), and of hippocampal
650 processing (Summerfield et al., 2006). Such top-down modulation is consistent with other evidence
651 that the regions engaged in pattern separation or completion vary according to the orienting task as
652 well as the stimuli (Hashimoto et al., 2012; Motley and Kirwan, 2012). Parametric analysis indicated
653 both conceptual and perceptual pattern separation in the right inferior frontal region. A contribution of
654 both similarity dimensions is in keeping with the task goals which made both dimensions of
655 individual items relevant. However a dominance of conceptual separation in the posterior LIFG ROI
656 may also reflect its proposed specialisation for resolution of competition between active semantic
657 representations (Badre et al., 2005; Thompson-Schill et al., 1999). The present data raise the
658 possibility that pattern separation computations may contribute to this resolution.

659 Suggestions of pattern completion from initial contrasts in regions including anterior inferior
660 left PFC, right precuneus and left parietal lobe were not borne out by the more specific parametric
661 similarity analysis. In the case of the left prefrontal regions, lack of significant repetition sensitivity
662 when only the subset of novel and repeated items were analysed precluded examination of input
663 response functions. Other repetition sensitive ROIs did overlap with clusters revealed in the overall
664 pattern separation (e.g., left and right middle occipital, right inferior occipital) or completion (left
665 inferior parietal, right precuneus) contrasts, but did not show the predicted model fit for these
666 computations. Selection of repetition sensitive ROIs using different trials from those included in
667 similarity analyses allowed us to ensure that the two pattern separation/completion analyses were
668 independent, but this reduced the number of trials in both analyses. Although this presumably
669 impacted sensitivity, the only inconsistent result between the two was in the right middle occipital *a*
670 *priori* ROI, in which the two analyses showed repetition effects of opposite direction. No region
671 showed greater evidence for a linear response than for the increasing/decreasing slope power
672 functions predicted for pattern separation or completion in the closest or overlapping peak. Future
673 studies examining response functions in *a priori* ROIs centred on the pattern separation and

674 completion regions revealed in the present overall analyses may observe supporting evidence of these
675 processes.

676   We did not find clear-cut evidence for either hippocampal pattern separation or completion,
677 despite previous findings (e.g., Bakker et al., 2008; O'Reilly and McClelland, 1994). The lower
678 spatial resolution here compared to previous fMRI studies of hippocampal pattern separation (Bakker
679 et al., 2008; Yassa et al., 2011) is the most likely explanation, as the current data did not permit
680 anatomical separation of responses in the hippocampal subregions in which pattern separation (DG)
681 and completion (CA1) signals have previously been reported (e.g., Hunsaker and Kesner, 2013;
682 Leutgeb et al., 2007).

683

684 **4.3 Item-specific and gist encoding**

685   Regions active at encoding differed according to whether subsequent memory was item-
686 specific, i.e., accurate recognition of studied items or mnemonic discrimination of lures; or gist-based,
687 i.e., false recognition of lures or partial recognition of studied items. Occipito-temporal regions
688 including left middle occipital cortex showed greater activity for encoding supporting accurate
689 recognition as opposed to gist memory, consistent with reports that visual processing supports later
690 item-specific memory for visually presented stimuli (Baym and Gonsalves, 2010; Kim and Cabeza,
691 2007; Kim, 2011). Posterior LIFG was also found to be engaged in encoding predicting accurate
692 recognition, consistent with Kim's (2011) meta-analysis of 74 subsequent memory studies.

693   We provide the first fMRI examination of encoding activity specific to subsequent mnemonic
694 discrimination of lures. Garoff et al. (2005) used the same retrieval task, but assumed that 'similar'
695 responses to lures may rely on either specific or gist memory, and so did not examine encoding linked
696 specifically to this response category. However, others have argued that mnemonic discrimination of
697 lures depends more than accurate recognition on item-specific encoding (Tun et al., 1998; see
698 Introduction). Only one cortical region was associated with subsequent lure discrimination, in left
699 posterior cingulate gyrus. The paucity of cortical responses observed to predict mnemonic
700 discrimination may reflect some lack of sensitivity, but it is also possible that this recognition
701 outcome in fact depends more on retrieval than on encoding processing, or relies more heavily on
702 hippocampal encoding processes, such as pattern separation, than cortical encoding (Yassa and Stark,
703 2011). Indeed, right posterior and left anterior hippocampus showed greater activity during encoding
704 predicting later mnemonic discrimination compared to later gist memory, supporting a critical role for
705 this region in mnemonic discrimination.

706   Left inferior parietal cortex and left posterior hippocampus showed greater activity during
707 encoding predicting later gist memory compared to lure correct rejection. Garoff et al. (2005)
708 identified a similar left inferior parietal region using similar contrasts, and proposed that activity in
709 this and other bilateral frontal and parietal regions reflected elaborative processing of semantic

710 information at encoding, contributing to subsequent reliance on gist information (Buckner et al.,
711 1998). The cluster in left posterior hippocampus is also close to a region previously linked to
712 subsequent recollection of gist (Manelis et al., 2013), supporting assumptions that false recognition is
713 often driven by overlapping gist (Brainerd and Reyna, 2002).

714   Fewer regions were associated with gist encoding here than in Garoff et al.'s (2005)
715 investigation, in which multiple bilateral cortical regions showed activity increases for gist encoding
716 compared to both item-specific encoding and subsequent forgetting. A notable difference between the
717 two studies is that Garoff et al. (2005) examined only encoding trials associated with later recognition
718 responses which were rated as highly confident, whereas here, all encoding trials associated with a
719 later 'same/similar/new' response were included in analyses. Garoff et al.'s (2005) wider cortical
720 engagement in gist encoding may reflect this difference. Alternatively, the greater rate of partial
721 recognition of studied items in Garoff et al.'s (2005) study (see Section 4.1.) may have meant that
722 their findings for gist encoding reflected forgetting to a greater degree than in the present study.
723

4.4. Pattern separation/ completion and encoding

725   Bilateral inferior frontal cortex and left middle occipital cortex were found to be active in
726 conjoint contrasts of pattern separation and encoding predicting subsequent hits (Table 7). In RIFG,
727 curve fitting analysis provided further support for conceptual and perceptual pattern separation. These
728 findings are consistent with the suggestion that cortical pattern separation at encoding contributes to
729 accurate recognition memory (e.g., Sahay et al., 2011; Schacter et al., 1998; Stark et al., 2013 Wilson
730 et al., 2006). The assignment of unique neural representations to novel input (pattern separation) may
731 aid formation of item-specific memory traces which later enable successful recognition of studied
732 items (Kirwan and Stark, 2007). Regions in the ventral visual stream are thought to represent object
733 features at increasing levels of complexity (Cowell et al., 2010a), and lesion data suggest that these
734 representations contribute to recognition memory (Cowell et al., 2010b; Norman and Eacott, 2004).
735 According to this hierarchical view, the occipital region showing functional overlap may contribute to
736 encoding of unique visual representations via pattern separation. Pattern separation occurring in the
737 ventral visual processing stream might influence the degree of pattern separation occurring within the
738 hippocampus and thus impact on recognition outcomes, or may contribute independently to
739 recognition (Cowell et al., 2010b; Yassa and Stark, 2011). The data are likewise consistent with the
740 notion that pattern separation in bilateral inferior PFC supports later recognition. One possibility is
741 that the resolution of interference between overlapping representations may contribute to item-specific
742 encoding. However while the functional overlap we observe goes beyond existing data in supporting
743 the proposed contribution of pattern separation to successful encoding, further, more direct evidence
744 is required to provide more robust support. This is particularly true in occipital cortex, in which there
745 was no converging evidence of pattern separation from the input similarity analyses. First, as

746 discussed in Section 4.2., more sensitive assessment of input similarity response functions in these
747 regions of overlap is needed in independent samples. Second, demonstration of stronger pattern
748 separation effects at encoding for items which are later correctly recognised compared to those which
749 are later forgotten would provide a clearer indication that the strength of pattern separation contributes
750 to these subsequent memory outcomes. Limited trial numbers and the fact that similar items presented
751 at study were not repeated at test meant this could not be assessed in the current study, but these are
752 important directions for future investigations.

753 Contrary to our predictions, encoding activity predicting subsequent lure mnemonic
754 discrimination did not engage any cortical regions which also showed evidence of pattern separation.
755 As noted above, mnemonic discrimination may rely to a greater extent on hippocampal pattern
756 separation at encoding than on cortical pattern separation. As we did not detect hippocampal pattern
757 separation, overlap with later mnemonic discrimination could not be directly assessed. A critical role
758 of the hippocampus in encoding supporting later mnemonic discrimination is however suggested by
759 neuropsychological and ageing studies (e.g., McHugh et al., 2007; Yassa et al., 2010), and is
760 consistent with our findings of hippocampal engagement in encoding predicting lure discrimination. It
761 is possible that the occipital and PFC regions identified here as involved in pattern separation
762 contribute to representing items uniquely, avoiding catastrophic interference in memory and enabling
763 later recognition. However, it is likely that further processing performed on the hippocampus' multi-
764 dimensional and contextual representations (Cowell et al., 2010a; Ranganath, 2010) also critically
765 influences later explicit mnemonic discrimination of similar lures.

766

767 **4.5. Limitations and future directions**

768 The current study provides the first evidence in humans of computational pattern separation and
769 pattern completion in cortical regions, the data are consistent with the view that cortical pattern
770 separation contributes to memory encoding. However while the overall analysis comparing activity
771 for similar items with that for repeated and novel items revealed activity consistent with the
772 computational properties of pattern separation or completion (Kumaran and Maguire, 2009), it
773 remains possible that it reflects other memory-related processes. Even in an incidental task, some
774 explicit recognition may have been triggered by repeated and similar items at study, and it is possible
775 that novel, similar and repeated items systematically differed in the degree of elaborative encoding
776 elicited. . The prefrontal regions revealed in the pattern separation contrasts have been implicated in
777 episodic retrieval (see Kim, 2013 for meta-analysis), as well as in semantic elaboration at encoding
778 (Dobbins et al., 2002; Han et al., 2012). However, both accounts would predict lure responses
779 intermediate in magnitude between responses to novel items and repetitions. Retrieval of the study
780 episode would presumably be triggered most frequently by repetitions, less frequently by lures, and
781 less again by novel items. It is also likely novel items would elicit the greatest semantic elaboration,

782   and repeated items the least. The pattern separation account on the other hand uniquely predicts that
783   on average, similar items show equivalent activity to novel items (or repeated items in the case of
784   pattern completion), and makes specific computational predictions relating to response functions to
785   parametrically varied input similarity. In parametric analyses, there was little evidence of the linear
786   pattern which would be expected if the encoding data were explained by a retrieval or elaborative
787   encoding account. A further possibility is that the responses in regions revealed in pattern separation
788   and completion contrasts reflect relative novelty or familiarity. However this too would predict a
789   linear response (Carr et al., 2010), and is therefore inconsistent with our findings.

790   In line with previous definitions of pattern separation, we operationalized these processes in
791   terms of the equivalence and difference of their neural responses to repeated, similar and novel (e.g.,
792   Bakker et al., 2008). However, unlike previous studies our analysis was unconstrained by the
793   direction of the repetition suppression or enhancement effect, rather than limited to regions showing
794   repetition suppression (e.g., Bakker et al., 2008; Lacy et al., 2011). Our inclusion of regions showing
795   repetition enhancement was exploratory, but in some cases – just as for regions showing repetition
796   suppression – was supported by findings of the predicted parametric response functions. It would be
797   of interest to determine whether future high resolution fMRI studies show this pattern of activity
798   within the hippocampal subregions known to be associated with pattern separation and completion.

799   Because of the nature of the BOLD signal, the parametric fMRI analyses can provide only
800   relatively indirect measures of pattern separation and completion compared to direct neuronal
801   recordings (Hunsaker and Kesner, 2013). Converging evidence of these processes in human studies
802   could also be provided by representational similarity analysis (Kriegeskorte et al., 2008). Given *a*
803   *priori* data regarding connectivity, representational similarity of novel and similar items could be
804   compared between pattern separation/ completion regions and their input regions. Evidence of
805   reduced representational similarity for a region relative to its input region would support the presence
806   of pattern separation, while increased representational similarity would support pattern completion.

807   The present data are consistent with the notion that cortical pattern separation contributes to
808   successful encoding. However, the fact that several regions showed cortical encoding-related activity
809   which predicted item-specific outcomes but did not show evidence of pattern separation or completion
810   – although these are null results – suggests that encoding mechanisms other than pattern separation
811   also contribute to recognition memory. This is as expected based on the fuzzy-trace theory view that
812   recognition failure reflects reliance on gist traces, formed as a result of semantic overlap between
813   studied episodes (Brainerd and Reyna, 2002). In principle, the fuzzy trace account is compatible with
814   a critical role for cortical pattern separation in reducing semantic overlap at the time of encoding
815   (Winocur et al., 2010; Wilson et al., 2006; Yassa and Reagh, 2013; see also Pidgeon and Morcom,
816   2014), but in the current study, we did not find clear evidence for such a role. Although one region in
817   RIFG showed both conceptual pattern separation responses and item-specific encoding activity, it also
818   showed perceptual pattern separation responses. However, we were not able to assess perceptual and

conceptual pattern separation systematically in regions overlapping with the encoding-related contrast, since these were not revealed in the repetition sensitivity contrasts. In other regions a stronger tendency for reduction of conceptual relative to perceptual similarity was hinted at in the curve fitting analyses: right parietal and left inferior frontal regions showed activity consistent with conceptual but not perceptual pattern separation, and no regions showed evidence of perceptual pattern separation alone. Future studies can more directly assess this proposal by examining the specific relation between semantic similarity and the success of later mnemonic discrimination in the regions implicated here in both pattern separation and specific memory encoding.

4.6. Conclusions

Our data suggest that pattern separation and pattern completion of perceptually and conceptually similar object representations extends beyond the hippocampus to prefrontal and occipito-temporal regions, supporting claims that these processes occur throughout the brain (Aimone et al., 2011; Barnes et al., 2008). By examining neural response to images varied in their similarity relative to previously viewed images, we provide evidence that the neural responses in several regions met computational predictions for pattern separation or completion for either or both perceptual and conceptual similarity. The further finding that some regions showed activity consistent with both pattern separation and item-specific encoding is consistent with the notion that these computations in cortex contribute to episodic memory.

References

Aimone, J. B., Deng, W., & Gage, F. H. (2011). Resolving New Memories: A Critical Look at the Dentate Gyrus, Adult Neurogenesis, and Pattern Separation. *Neuron, 70*(4), 589-596. doi: 10.1016/j.neuron.2011.05.010

855 Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *Neuroimage, 26*(3), 839-851. doi:
856   10.1016/j.neuroimage.2005.02.018
857 Badre, D., Poldrack, R. A., Pare-Blagoev, E. J., Insler, R. Z., & Wagner, A. D. (2005). Dissociable controlled
858   retrieval and generalized selection mechanisms in ventrolateral prefrontal cortex. *Neuron, 47*(6), 907-
859   918. doi: 10.1016/j.neuron.2005.07.023
860 Badre, D., & Wagner, A. D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory.
861   *Neuropsychologia, 45*(13), 2883-2901. doi: 10.1016/j.neuropsychologia.2007.06.015
862 Bakker, A., Kirwan, C. B., Miller, M., & Stark, C. E. L. (2008). Pattern separation in the human hippocampal
863   CA3 and dentate gyrus. *Science, 319*(5870), 1640-1642. doi: 10.1126/science.1152882
864 Barnes, D. C., Hofacer, R. D., Zaman, A. R., Rennaker, R. L., & Wilson, D. A. (2008). Olfactory perceptual
865   stability and discrimination. *Nature Neuroscience, 11*(12), 1378-1380. doi: 10.1038/nn.2217
866 Baym, C. L., & Gonsalves, B. D. (2010). Comparison of neural activity that leads to true memories, false
867   memories, and forgetting: An fMRI study of the misinformation effect. *Cognitive Affective & Behavioral*
868   *Neuroscience, 10*(3), 339-348. doi: 10.3758/cabn.10.3.339
869 Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where Is the Semantic System? A Critical
870   Review and Meta-Analysis of 120 Functional Neuroimaging Studies. *Cerebral Cortex, 19*(12), 2767-2796.
871   doi: 10.1093/cercor/bhp055
872 Boccardi, M., Ganzola, R., Bocchetta, M., Pievani, M., Redolfi, A., Bartzokis, G., Frisoni, G. B. (2011). Survey
873   of protocols for the manual segmentation of the hippocampus: preparatory steps towards a joint EADC-
874   ADNI harmonized protocol. *Journal of Alzheimers Disease, 26*, 61-75. doi: 10.3233/jad-2011-0004
875 Brainerd, C. J., & Reyna, V. F. (1990). Gist is the grist - Fuzzy-trace theory and the new intuitionism.
876   *Developmental Review, 10*(1), 3-47. doi: 10.1016/0273-2297(90)90003-m
877 Brainerd, C. J., & Reyna, V. F. (2002). Fuzzy-trace theory and false memory. *Current Directions in*
878   *Psychological Science, 11*(5), 164-169. doi: 10.1111/1467-8721.00192
879 Brainerd, C. J., Reyna, V. F., Wright, R., & Mojardin, A. H. (2003). Recollection rejection: False-memory
880   editing in children and adults. *Psychological Review, 110*(4), 762-784. doi: 10.1037/0033-
881   295x.110.4.762
882 Burnham, K. P., & Anderson, D. R. (1998). Model selection and inference: a practical information-theoretic
883   approach. London: Springer.
884 Buckner, R. L., Koutstaal, W., Schacter, D. L., Wagner, A. D., & Rosen, B. R. (1998). Functional-anatomic
885   study of episodic retrieval using fMRI. *Neuroimage, 7*, 151-162.
886 Carr, V. A., Rissman, J., & Wagner, A. D. (2010). Imaging the human medial temporal lobe with high-
887   resolution fMRI. *Neuron, 65*(3), 298-308. doi: 10.1016/j.neuron.2009.12.022
888 Cheng, S.-K., & Rugg, M. D. (2010). Event-related potential correlates of gist and verbatim encoding.
889   *International Journal of Psychophysiology, 77*(2), 95-105. doi: 10.1016/j.ijpsycho.2010.04.010
890 Chouinard, P. A., Morrissey, B. F., Kohler, S., & Goodale, M. A. (2008). Repetition suppression in occipital-
891   temporal visual areas is modulated by physical rather than semantic features of objects. *Neuroimage, 41*(1),
892   130-144. doi: 10.1016/j.neuroimage.2008.02.011
893 Cowell, R. A., Bussey, T. J., & Saksida, L. M. (2010a). Components of Recognition Memory: Dissociable
894   Cognitive Processes or Just Differences in Representational Complexity? *Hippocampus, 20*(11), 1245-1262.
895   doi: 10.1002/hipo.20865
896 Cowell, R. A., Bussey, T. J., & Saksida, L. M. (2010b). Functional Dissociations within the Ventral Object
897   Processing Pathway: Cognitive Modules or a Hierarchical Continuum? *Journal of Cognitive Neuroscience,*
898   *22*(11), 2460-2479. doi: 10.1162/jocn.2009.21373
899 Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance
900   neuroimages. *Computers and Biomedical Research, 29*(3), 162-173. doi: 10.1006/cbmr.1996.0014
901 Dudukovic, N. M., & Wagner, A. D. (2007). Goal-dependent modulation of declarative memory: Neural
902   correlates of temporal recency decisions and novelty detection. *Neuropsychologia, 45*(11), 2608-2620. doi:
903   10.1016/j.neuropsychologia.2007.02.025
904 Fairhall, S. L., Anzellotti, S., Pajtas, P. E., & Caramazza, A. (2011). Concordance between perceptual and
905   categorical repetition effects in the ventral visual stream. *Journal of Neurophysiology, 106*(1), 398-408. doi:
906   10.1152/jn.01138.2010
907 Fisher, R. A. (1950). Statistical methods for research workers, Ed. 11. London: Oliver and Boyd.
908 Foo, T.F., Grigsby, N.S., Mitchell, J.D., & Slayman, B.E. (1994). SNORE: Spike Noise Removal and Detection.
909   *IEEE Transactions on Medical Imaging, 13*(1): 133-136.
910 Friston, K.J., Glaser, D.E., Henson, R.N., Kiebel, S., Phillips, C. & Ashburner, J. (2002). Classical and Bayesian
911   inference in neuroimaging: applications. *Neuroimage.* 16,484-512.
912 Friston, K. J., Williams, S., Howard, R., Frackowiak, R. S. J., & Turner, R. (1996). Movement-related effects in
913   fMRI time-series. *Magnetic Resonance in Medicine, 35*(3), 346-355. doi: 10.1002/mrm.1910350312

914 Garoff, R. J., Slotnick, S. D., & Schacter, D. L. (2005). The neural origins of specific and general memory: the
915   role of the fusiform cortex. *Neuropsychologia, 43*(6), 847-859. doi: 10.1016/j.neuropsychologia.2004.09.014
916 Geng, H., Qi, Y., Li, Y., Fan, S., Wu, Y., & Zhu, Y. (2007). Neurophysiological correlates of memory illusion
917   in both encoding and retrieval phases. *Brain Research, 1136*(1), 154-168. doi:
918   10.1016/j.brainres.2006.12.027
919 Gilbert, P. E., & Kesner, R. P. (2003). Recognition memory for complex visual discriminations is influenced by
920   stimulus interference in rodents with perirhinal cortex damage. *Learning & Memory, 10*(6), 525-530. doi:
921   10.1101/lm.64503
922 Gilbert, P. E., Kesner, R. P., & Lee, I. (2001). Dissociating hippocampal subregions: A double dissociation
923   between dentate gyrus and CA1. *Hippocampus, 11*(6), 626-636. doi: 10.1002/hipo.1077
924 Goodrich-Hunsaker, N. J., Hunsaker, M. R., & Kesner, R. P. (2008). The interactions and dissociations of the
925   dorsal hippocampus subregions: How the dentate gyrus, CA3, and CA1 process spatial information.
926   *Behavioral Neuroscience, 122*(1), 16-26. doi: 10.1037/0735-7044.122.1.16
927 Gutchess, A. H., & Schacter, D. L. (2012). The neural correlates of gist-based true and false recognition.
928   *Neuroimage, 59*(4), 3418-3426. doi: 10.1016/j.neuroimage.2011.11.078
929 Guzowski, J. F., Knierim, J. J., & Moser, E. I. (2004). Ensemble dynamics of hippocampal regions CA3 and
930   CA1. *Neuron, 44*(4), 581-584. doi: 10.1016/j.neuron.2004.11.003
931 Hashimoto, R., Abe, N., Ueno, A., Fujii, T., Takahashi, S., & Mori, E. (2012). Changing the criteria for old/new
932   recognition judgements can modulate activity in the anterior hippocampus. *Hippocampus, 22*(2), 141-148.
933   doi: 10.1002/hipo.20878
934 Henson, R. N. A., & Rugg, M. D. (2003). Neural response suppression, haemodynamic repetition effects, and
935   behavioural priming. *Neuropsychologia, 41*(3), 263-270. doi: Pii s0028-3932(02)00159-810.1016/s0028-
936   3932(02)00159-8
937 Horner, A. J., & Henson, R. N. (2011). Repetition suppression in occipitotemporal cortex despite negligible
938   visual similarity: Evidence for postperceptual processing? *Human Brain Mapping, 32*(10), 1519-1534. doi:
939   10.1002/hbm.21124
940 Hunsaker, M. R., & Kesner, R. P. (2013). The operation of pattern separation and pattern completion processes
941   associated with different attributes or domains of memory. *Neuroscience and Biobehavioral Reviews, 37*(1),
942   36-58. doi: 10.1016/j.neubiorev.2012.09.014
943 Kim, H. (2011). Neural activity that predicts subsequent memory and forgetting: A meta-analysis of 74 fMRI
944   studies. *Neuroimage, 54*(3), 2446-2461. doi: 10.1016/j.neuroimage.2010.09.045
945 Kim, H. (2013). Differential neural activity in the recognition of old versus new events: An activation likelihood
946   estimation meta-analysis. *Human Brain Mapping, 34*(4), 814-836. doi: 10.1002/hbm.21474
947 Kim, J. G., Biederman, I., Lescroart, M. D., & Hayworth, K. J. (2009). Adaptation to objects in the lateral
948   occipital complex (LOC): Shape or semantics? *Vision Research, 49*(18), 2297-2305. doi:
949   10.1016/j.visres.2009.06.020
950 Kim, H., & Cabeza, R. (2007). Differential contributions of prefrontal, medial temporal, and sensory-perceptual
951   regions to true and false memory formation. *Cerebral Cortex, 17*(9), 2143-2150. doi: 10.1093/cercor/bhl122
952 Kirwan, C. B., Hartshorn, A., Stark, S. M., Goodrich-Hunsaker, N. J., Hopkins, R. O., & Stark, C. E. L. (2012).
953   Pattern separation deficits following damage to the hippocampus. *Neuropsychologia, 50*(10), 2408-2414.
954   doi: 10.1016/j.neuropsychologia.2012.06.011
955 Kirwan, C. B., & Stark, C. E. L. (2007). Overcoming interference: An fMRI investigation of pattern separation
956   in the medial temporal lobe. *Learning & Memory, 14*(9), 625-633. doi: 10.1101/lm.663507
957 Konkle, T., Brady, T. F., Alvarez, G. A., & Oliva, A. (2010). Conceptual distinctiveness supports detailed visual
958   long-term memory for real-world objects. *Journal of Experimental Psychology-General, 139*(3), 558-578.
959   doi: 10.1037/a0019165
960 Koutstaal, W. (2006). Flexible remembering. *Psychonomic Bulletin & Review, 13*(1), 84-91. doi:
961   10.3758/bf03193817
962 Koutstaal, W., & Schacter, D. L. (1997). Gist-based false recognition of pictures in older and younger adults.
963   *Journal of Memory and Language, 37*(4), 555-583. doi: 10.1006/jmla.1997.2529
964 Koutstaal, W., Schacter, D. L., Galluccio, L., & Stofer, K. A. (1999). Reducing gist-based false recognition in
965   older adults: Encoding and retrieval manipulations. *Psychology and Aging, 14*(2), 220-237. doi:
966   10.1037/0882-7974.14.2.220
967 Koutstaal, W., Wagner, A. D., Rotte, M., Maril, A., Buckner, R. L., & Schacter, D. L. (2001). Perceptual
968   specificity in visual object priming: functional magnetic resonance imaging evidence for a laterality
969   difference in fusiform cortex. *Neuropsychologia, 39*(2), 184-199. doi: 10.1016/s0028-3932(00)00087-7
970 Kriegeskorte, N., Mur, M., & Bandettini, P. (2008). Representational similarity analysis – Connecting the
971   branches of systems neuroscience. *Frontiers in Systems Neuroscience, 2*, 4. doi: 10.3389/neuro.06.004.2008

972 Kubota, Y., Toichi, M., Shimizu, M., Mason, R. A., Findling, R. L., Yamamoto, K., & Calabrese, J. R. (2006).
973   Prefrontal hemodynamic activity predicts false memory - A near-infrared spectroscopy study. *Neuroimage,*
974   *31*(4), 1783-1789. doi: 10.1016/j.neuroimage.2006.02.003

975 Kumaran, D., & Maguire, E. A. (2009). Novelty signals: A window into hippocampal information processing.
976   *Trends in Cognitive Sciences, 13*(2), 47-54. doi: 10.1016/j.tics.2008.11.004

977 Lacy, J. W., Yassa, M. A., Stark, S. M., Muftuler, L. T., & Stark, C. E. L. (2011). Distinct pattern separation
978   related transfer functions in human CA3/dentate and CA1 revealed using high-resolution fMRI and variable
979   mnemonic similarity. *Learning & Memory, 18*(1), 15-18. doi: 10.1101/lm.1971110

980 Lazar, N.A., Luna, B., Sweeney, J.A., & Eddy, W.F. (2002) Combining brains: a survey of methods for
981   statistical pooling of information. *NeuroImage* 16:538 –550.

982 Lee, A. C. H., Bandelow, S., Schwarzbauer, C., Henson, R. N. A., & Graham, K. S. (2006). Perirhinal cortex
983   activity during visual object discrimination: An event-related fMR1 study. *Neuroimage, 33*(1), 362-373. doi:
984   10.1016/j.neuroimage.2006.06.021

985 Leutgeb, J. K., Leutgeb, S., Moser, M. B., & Moser, E. I. (2007). Pattern separation in the dentate gyrus and
986   CA3 of the hippocampus. *Science, 315*(5814), 961-966. doi: 10.1126/science.1135801

987 Machluf, S. (2008). Curve fitting in Matlab. Retrieved September 9, 2014 from
988   http://physweb.bgu.ac.il/~machlufs/files/CFTool_Tutorial.pdf

989 Manelis, A., Paynter, C. A., Wheeler, M. E., & Reder, L. M. (2013). Repetition related changes in activation and
990   functional connectivity in hippocampus predict subsequent memory. *Hippocampus, 23*(1), 53-65. doi:
991   10.1002/hipo.22053

992 Marr, D. (1971). Simple memory - Theory for archicortex. *Philosophical Transactions of the Royal Society of*
993   *London Series B-Biological Sciences, 262*(841), 23-81. doi: 10.1098/rstb.1971.0078

994 McHugh, T. J., Jones, M. W., Quinn, J. J., Balthasar, N., Coppari, R., Elmquist, J. K., . . . Tonegawa, S. (2007).
995   Dentate gyrus NMDA receptors mediate rapid pattern separation in the hippocampal network. *Science,*
996   *317*(5834), 94-99. doi: 10.1126/science.1140263

997 McNaughton, B. L., & Morris, R. G. M. (1987). Hippocampal synaptic enhancement and information-storage
998   within a distributed memory system. *Trends in Neurosciences, 10*(10), 408-415. doi: 10.1016/0166-
999   2236(87)90011-7

1000 Morcom, A.M. (2015). Resisting false recognition: An ERP study of lure discrimination. *Brain Research, 1624,*
1001   336-348. doi:10.1016/j.brainres.2015.07.049

1002 Motley, S. E., & Kirwan, C. B. (2012). A parametric investigation of pattern separation processes in the medial
1003   temporal lobe. *Journal of Neuroscience, 32*(38), 13076-U13378. doi: 10.1523/jneurosci.5920-11.2012

1004 Norman, G., & Eacott, M.J. (2004). Impaired object recognition with increasing levels of feature ambiguity in
1005   rats with perirhinal cortex lesions. *Behavioral Brain Research, 148*, 79-91. doi: 10.1016/S0166-
1006   4328(03)00176-1

1007 Norman, K. A. (2010). How hippocampus and cortex contribute to recognition memory: Revisiting the
1008   complementary learning systems model. *Hippocampus, 20*(11), 1217-1227. doi: 10.1002/hipo.20855

1009 Norman, K. A., & O'Reilly, R. C. (2003). Modeling hippocampal and neocortical contributions to recognition
1010   memory: A complementary-learning-systems approach. *Psychological Review, 110*(4), 611-646. doi:
1011   10.1037/0033-295x.110.4.611

1012 O'Reilly, R. C., & McClelland, J. L. (1994). Hippocampal conjunctive encoding, storage, and recall - avoiding a
1013   trade-off. *Hippocampus, 4*(6), 661-682. doi: 10.1002/hipo.450040605

1014 Penny, W., & Holmes, A. (2006). Random effects analysis. In K. Friston, J. Ashburner, S. Kiebel, T. Nichols, &
1015   W. Penny (Eds.), *Statistical parametric mapping: The analysis of functional brain images* (pp. 156–165).
1016   London: Elsevier.

1017 Pidgeon, L.M. & Morcom, A.M. (2014). Age-related increases in false recognition: The role of perceptual and
1018   conceptual similarity. *Frontiers in Aging Neuroscience, 6*:283. doi: 10.3389/fnagi.2014.00283

1019 Ranganath, C. (2010). A unified framework for the functional organization of the medial temporal lobes and the
1020   phenomenology of episodic memory. *Hippocampus, 20*(11), 1263-1290. doi: 10.1002/hipo.20852

1021 Roediger, H. L., & McDermott, K. B. (1995). Creating false memories - Remembering words not presented in
1022   lists. *Journal of Experimental Psychology-Learning Memory and Cognition, 21*(4), 803-814. doi:
1023   10.1037/0278-7393.21.4.803

1024 Rolls, E.T. (1996). A theory of hippocampal function in memory. *Hippocampus, 6*, 601-620. doi:

1025 Rolls, E. T. (2007). An attractor network in the hippocampus: theory and neurophysiology. *Learn. Mem.* 14,
1026   714–731. doi:10.1101/lm.631207

1027 Sahay, A., Scobie, K. N., Hill, A. S., O'Carroll, C. M., Kheirbek, M. A., Burghardt, N. S., . . . Hen, R. (2011).
1028   Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature, 472*(7344),
1029   466-U539. doi: 10.1038/nature09817

1030 Schacter, D. L., Norman, K. A., & Koutstaal, W. (1998). The cognitive neuroscience of constructive memory.
1031   *Annual Review of Psychology, 49*, 289-318. doi: 10.1146/annurev.psych.49.1.289

Stark, C. E. L., & Okado, Y. (2003). Making memories without trying: Medial temporal lobe activity associated with incidental memory formation during recognition. *Journal of Neuroscience, 23*(17), 6748-6753.

Stark, S. M., Yassa, M. A., Lacy, J. W., & Stark, C. E. L. (2013). A task to assess behavioral pattern separation (BPS) in humans: Data from healthy aging and mild cognitive impairment. *Neuropsychologia, 51*(12), 2442-2449. doi: 10.1016/j.neuropsychologia.2012.12.014

Stenberg, G., Hellman, J., Johansson, M., & Rosen, I. (2009). Familiarity or conceptual priming: Event-related potentials in name recognition. *Journal of Cognitive Neuroscience, 21*(3), 447-460. doi:10.1162/jocn.2009.21045

Summerfield, C., Greene, M., Wager, T., Egner, T., Hirsch, J., & Mangels, J. (2006). Neocortical connectivity during episodic memory formation. *PLoS Biology, 4*(5), e128. Doi:10.1371/journal.pbio.0040128

Thompson-Schill, S. L., D'Esposito, M., & Kan, I. P. (1999). Effects of repetition and competition on activity in left prefrontal cortex during word generation. *Neuron 23*(3), 513-522. doi:10.1016/S0896-6273(00)80804-1

Toner, C. K., Pirogovsky, E., Kirwan, C. B., & Gilbert, P. E. (2009). Visual object pattern separation deficits in nondemented older adults. *Learning & Memory, 16*(5), 338-342. doi: 10.1101/lm.1315109

Treves, A., & Rolls, E. T. (1992). Computational constraints suggest the need for 2 distinct input systems to the hippocampal CA3-network. *Hippocampus, 2*(2), 189-200. doi: 10.1002/hipo.450020209

Tun, P. A., Wingfield, A., Rosen, M. J., & Blanchard, L. (1998). Response latencies for false memories: Gist-based processes in normal aging. *Psychology and Aging, 13*(2), 230-241. doi: 10.1037//0882-7974.13.2.230

Urbach, T. P., Windmann, S. S., Payne, D. G., & Kutas, M. (2005). Mismaking memories - Neural precursors of memory illusions in electrical brain activity. *Psychological Science, 16*(1), 19-24. doi: 10.1111/j.0956-7976.2005.00775.x

Vazdarjanova, A., & Guzowski, J. F. (2004). Differences in hippocampal neuronal population responses to modifications of an environmental context: Evidence for distinct, yet complementary, functions of CA3 and CA1 ensembles. *Journal of Neuroscience, 24*(29), 6489-6496. doi: 10.1523/jneurosci.0350-04.2004

Vercauteren, T., Pennec, X., Perchant, A., & Ayache, N. (2007). Non-parametric diffeomorphic image registration with the demons algorithm. Medical image computing and computer-assisted intervention : MICCAI ... *International Conference on Medical Image Computing and Computer-Assisted Intervention, 10(Pt 2)*, 319-326.

Wilson, D. A. (2009). Pattern separation and completion in olfaction. *International Symposium on Olfaction and Taste, 1170*, 306-312. doi: 10.1111/j.1749-6632.2009.04017.

Wilson, I. A., Gallagher, M., Eichenbaum, H., & Tanila, H. (2006). Neurocognitive aging: Prior memories hinder new hippocampal encoding. *Trends in Neurosciences, 29*(12), 662-670. doi: 10.1016/j.tins.2006.10.002

Winocur, G., Moscovitch, M., & Bontempi, B. (2010). Memory formation and long-term retention in humans and animals: Convergence towards a transformation account of hippocampal-neocortical interactions. *Neuropsychologia, 48*(8), 2339-2356. doi: 10.1016/j.neuropsychologia.2010.04.016

Yassa, M. A., Lacy, J. W., Stark, S. M., Albert, M. S., Gallagher, M., & Stark, C. E. L. (2011). Pattern separation deficits associated with increased hippocampal CA3 and dentate gyrus activity in nondemented older adults. *Hippocampus, 21*(9), 968-979. doi: 10.1002/hipo.20808

Yassa, M. A., Muftuler, L. T., & Stark, C. E. L. (2010). Ultrahigh-resolution microstructural diffusion tensor imaging reveals perforant path degradation in aged humans in vivo. *Proceedings of the National Academy of Sciences of the United States of America, 107*(28), 12687-12691. doi: 10.1073/pnas.1002113107

Yassa, M. A., & Reagh, Z. M. (2013). Competitive trace theory: A role for the hippocampus in contextual interference during retrieval. *Frontiers in Behavioral Neuroscience, 7*. doi: 10.3389/fnbeh.2013.00107

Yassa, M. A., & Stark, C. E. L. (2011). Pattern separation in the hippocampus. *Trends in Neurosciences, 34*(10), 515-525. doi: 10.1016/j.tins.2011.06.006

Yushkevich, P. A., Piven, J., Hazlett, H. C., Smith, R. G., Ho, S., Gee, J. C., & Gerig, G. (2006). User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. *Neuroimage, 31*(3), 1116-1128. doi: 10.1016/j.neuroimage.2006.01.015

Zanto, T.P., Rubens, M.T., Thangavel, A., Gazzaley, A. (2011). Causal role of the prefrontal cortex in top-down modulation of visual processing and working memory. *Nature Neuroscience, 14*(5), 656-663. Doi: 10.1038/nn.2773

Figure captions

Fig. 1. Predicted input-output response functions for pattern separation and pattern completion regions. S1 = high similarity items, S2 = medium similarity items, S3 = low similarity items. **A)** In regions showing repetition suppression, pattern separation is predicted to show a power function with decreasing slope in response to change in input, falling above the diagonal. Pattern completion regions are expected to fit an increasing slope power function, falling below the diagonal. **B)** In regions where repetitions show increased activity relative to novel items, functions in the opposite direction are predicted. Pattern separation is predicted to show a decreasing slope power function falling below the diagonal, and pattern completion an increasing slope power function falling above the diagonal. In **A)** and **B)**, the linear diagonal represents cases where change in input and change in output are equal. Adapted from Motley & Kirwan (2012).

1087

Fig. 2. Experimental procedure. At study, participants performed a size judgement task, judging whether each item would fit in a shoe box. Novel images, repetitions, and similar images were presented. At test, participants responded 'same', 'similar', 'new' or 'guess' to studied, lure and novel items (see Section 2.3. for details).

1088

Fig. 3. Proportions of 'same', 'similar' and 'new' responses to studied, lure and novel items during the recognition test. Means ± SE.

1089

Fig. 4. **Pattern separation in selected cortical regions.** A) Pattern separation (repetition < similar = novel) in right inferior temporal gyrus (peak [39, -61, -8]) and B) 'reverse' pattern separation (repetition > similar = novel) in right inferior parietal lobule (peak [50, -46, 28]). In bar plots, y-axes represent parameter estimates (arbitrary units). The plots show activity change (arbitrary units) ± SE in these regions to repeated (R), all similar (S) and novel (N) items relative to fixation at peak voxels of clusters revealed in whole-brain pattern separation contrasts (see Sections 2.7.1. and 3.2.1.1. for thresholding and analysis). Sections show activity superimposed on the SPM8 canonical T1 image.

1090
1091

Fig. 5. **Pattern completion in selected cortical regions.** A) Pattern completion activity (repetition = similar < novel) in left inferior frontal gyrus (peak [-48, 31, 8]) and B) 'reverse' pattern completion (repetition = similar > novel) in left superior frontal gyrus (peak [-24, 57, 1]). In bar plots, y-axes represent parameter estimates (arbitrary units). Plots show activity change (arbitrary units) ± SE in these regions to repeated (R), all similar (S) and novel (N) items relative to fixation at peak voxels of clusters revealed in whole-brain pattern separation contrasts (see Sections 2.7.1. and 3.2.1.1. for thresholding and analysis). Sections show activity superimposed on the SPM8 canonical T1 image.

1092
1093

Fig. 6. Best fitting curves for perceptual (blue) and conceptual (red) similarity in repetition sensitive (A-B) or a priori (C) ROIs. Data points reflect activity to repetitions (R), items of high (S1), medium (S2) and low (S3) perceptual or conceptual similarity (relative to previously viewed images), and 1st presentations of novel items (N). (A) RIFG (51, 8, 25), revealed in the novel > repeated contrast, showed the predicted decreasing slope power functions for both similarity measures, consistent with pattern separation. (B) R supramarginal gyrus (51, -52, 25) showed the predicted decreasing slope power function for conceptual similarity only, consistent with pattern separation. (C) The a priori posterior LIFG ROI (-37, 2, 31) showed the predicted decreasing slope power function for conceptual similarity only. Mean beta values ± SE. Model fit parameters are summarised in Table 5 and Table S1.

1097

Fig. 7. **Regions showing functional overlap between pattern separation and item-specific encoding.** Sections show activity superimposed on the SPM8 canonical T1 image. In bar plots, y-axes represent parameter estimates (arbitrary units). Plots of parameter estimates provide a visual illustration of the pattern of responses observed in these regions, but are not intended to contribute to any inference within these regions. (A) Plots show mean parameter estimates (arbitrary units) ± SE for conditions of interest in repetition < similar = novel (top row) and Hits > Gist (PR and FR; bottom row) contrasts (compared to baseline) in peak voxel of left inferior frontal cortex region [-45, 11, 22]. (B) Plots show mean parameter estimates (arbitrary units) for conditions of interest in repetition < similar = novel (top row) and Hits > PR of Studied items (bottom row) contrasts in peak voxel of left occipital region [-30, -88, -2]. See Section 3.2.4.1. for analysis strategy.

1098
1099