

## Human parahippocampal cortex supports spatial binding in visual working memory

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Keywords:	Visual working memory, Parahippocampal cortex, Spatial Memory, Medial temporal lobe, Feature binding

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3 **1 Human parahippocampal cortex supports spatial binding in visual working**  
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25 **Running title:** Human PHC supports spatial binding

1  
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3 26 **Abstract**

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5 27 Studies investigating the functional organisation of the medial temporal lobe (MTL)  
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7 28 suggest that parahippocampal cortex (PHC) generates representations of spatial and  
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10 29 contextual information used by the hippocampus in the formation of episodic  
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12 30 memories. However, evidence from animal studies also implicates PHC in spatial  
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14 31 binding of visual information held in short term, working memory. Here we examined  
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16 32 a 46-year-old man (PJ), after he had recovered from bilateral medial occipitotemporal  
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18 33 cortex strokes resulting in ischemic lesions of PHC and hippocampal atrophy, and a  
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21 34 group of age-matched healthy controls. When recalling the colour of one of two  
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23 35 objects, PJ misidentified the target when cued by its location, but not shape. When  
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25 36 recalling the position of one of three objects, he frequently misidentified the target,  
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27 37 which was cued by its colour. Increasing the duration of the memory delay had no  
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29 38 impact on the proportion of binding errors, but did significantly worsen recall  
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31 39 precision in both PJ and controls. We conclude that PHC may play a crucial role in  
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34 40 spatial binding during encoding of visual information in working memory.

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38 42 **Keywords:** Feature binding; Medial temporal lobe; Parahippocampal cortex; Spatial  
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40 43 Memory; Visual working memory  
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## 44 Introduction

45 The medial temporal lobe (MTL) comprises the hippocampus and parahippocampal  
46 regions, i.e., entorhinal cortex, perirhinal cortex (PRC) and parahippocampal cortex  
47 (PHC). These structures play a prominent role in episodic memory, as evidenced by  
48 the dense anterograde amnesia, which follows damage to MTL (Scoville and Milner  
49 1957; Corkin 1984; Corkin et al. 1997). Modular accounts of MTL function have  
50 suggested that the hippocampus synthesises episodic memories by binding  
51 information about the identity and location of objects carried respectively by two  
52 different streams (Eichenbaum et al. 2007; Diana et al. 2007).

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54 MTL structures have also been implicated in short term memory processes  
55 (Ranganath and Blumenfeld 2005; Graham et al. 2010; Yonelinas, 2013). First,  
56 animal models have pointed to specific molecular mechanisms in the mammalian  
57 MTL dedicated to the storage of short term memories, and separate from those  
58 involved in long term memory (Deacon et al. 2002; Reisel et al. 2002). Single unit  
59 recordings and lesion studies in non-human primates have further demonstrated that  
60 the hippocampus (Friedman and Goldman-Rakic 1988), entorhinal cortex (Suzuki et  
61 al. 1997), PRC (Davachi and Goldman-Rakic 2001) and PHC (Bachevalier and  
62 Nemanic 2008) contribute to the encoding and recall of information from short term  
63 memory. These animal findings complement neuropsychological studies of patients  
64 with amnesia resulting from Korsakoff's Syndrome, encephalitis and colloid cysts  
65 (Holdstock et al. 1995), and patients with surgical (Aggleton 1992; Owen et al. 1995)  
66 or ischemic (Holdstock et al. 2002) lesions to the MTL, demonstrating retention  
67 deficits for novel stimuli over delay intervals as short as two seconds (Ranganath  
68 and Blumenfeld 2005).

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5 70 An increasing body of evidence further suggests that short term memory exploits the  
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7 71 same MTL modules as episodic memory; that is, PRC codes information about an  
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10 72 object's identity and PHC codes an object's location and its context, and these two  
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12 73 streams are bound in the hippocampus (Pertzov et al. 2013; Watson et al. 2013; Yee et  
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14 74 al. 2014; Libby et al. 2014). Consistent with the idea that in short term memory  
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16 75 identity and location information are processed separately and then bound, patients  
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18 76 with hippocampal damage can exhibit deficits recalling object-location conjunctions  
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20 77 after 1.0s delays, even when unimpaired recalling either object identities or locations  
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22 78 (Olson et al. 2006a; 2006b). However, other studies report that patients with damage  
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24 79 to the hippocampus do not necessarily show deficits in recalling object-location  
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26 80 conjunctions, suggesting that spatial binding is preserved (e.g. Jenson et al. 2010; see  
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28 81 Yonelinas 2013 for a review).  
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34 83 An alternative possibility is that spatial binding in short term memory occurs in  
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36 84 parahippocampal regions, rather than the hippocampus proper. In support of this  
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38 85 view, data in both rats (Burwell and Amaral 1998) and monkeys (Suzuki and Amaral  
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40 86 1994) indicate that PRC and PHC are reciprocally connected, suggesting that the  
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42 87 parcellation of identity and spatial information is not absolute, and that there may  
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44 88 already be substantial cross-talk between object and spatial/context related  
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46 89 information in parahippocampal regions. Further, recordings in rats have  
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48 90 demonstrated single unit responses for object-location conjunctions in the PHC  
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50 91 homologue (Barker and Warburton 2011).  
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3 93 Behavioural studies in monkeys have provided crucial evidence for the role of PHC in  
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5 94 spatial binding. Rhesus monkeys with PHC lesions are impaired in both simple  
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7 95 location and object-location conjunction tasks (Malkova and Mishkin, 2003). This  
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10 96 short term memory impairment was observed in a delayed match-to-sample task,  
11  
12 97 where the sample contained two non-identical objects. After a six-second delay, the  
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14 98 test array contained one of the objects in its original location (the target), and an  
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16 99 identical item either at the location of the sample foil (object-place condition), or at a  
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18 100 novel location not previously occupied by either sample object (location condition).  
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21 101 Monkeys with PHC lesions were impaired identifying the target in both conditions,  
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23 102 while monkeys with lesions in the hippocampus showed no impairment in either task  
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25 103 (Malkova and Mishkin 2003). Hippocampectomised monkeys were likewise  
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27 104 unimpaired in a later study, using a more difficult task with an increased number of  
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29 105 objects and locations (Belcher et al. 2006).  
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34 107 A cross-species homology in the short term memory functionality of PHC is partly  
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36 108 supported by the observation that patients with PHC lesions also exhibit a decrement  
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38 109 in spatial recall (Ploner et al. 2000), although this impairment is only observed using  
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40 110 delays greater (i.e. >15.0s) than those used by Malkova and Mishkin (2003). In  
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42 111 addition, functional imaging data in healthy subjects demonstrate heightened right  
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44 112 PHC activation during both encoding and maintenance of object-location  
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46 113 conjunctions, relative to trials where objects or locations are memorised separately  
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48 114 (Luck et al. 2010). However, no neuropsychological study has so far demonstrated  
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50 115 that PHC contributes to spatial binding in human short term memory.  
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3 117 In the present study, we examined the nature and extent of spatial and short term  
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5 118 memory deficits associated with focal PHC lesions, by testing a middle-aged man (PJ)  
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7 119 with bilateral posterior circulation strokes involving the PHC, but sparing the  
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9 120 hippocampus and PRC. Our experiments were driven by three specific research  
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11 121 questions: 1) does damage to PHC produce binding difficulties and if so, are the  
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13 122 binding problems specifically spatial or do they generalise to other visual dimensions;  
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15 123 2) do binding impairments reflect deficits in memory encoding or maintenance; and  
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17 124 3) is the binding impairment secondary to a loss of positional information either in  
18  
19 125 memory or perception?  
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25 127 Both PJ and controls showed dependent decrements in the precision of spatial recall,  
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27 128 however PJ's recall precision was significantly worse than controls at longer delays  
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29 129 (5.0s). PJ also showed impaired spatial binding. This impairment was unaffected by  
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31 130 the duration of the memory delay. Finally, PJ's binding deficits did not generalise  
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33 131 across visual dimensions, since he performed normally when recall involved the  
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35 132 conjunction of non-spatial features. We conclude that PHC serves a spatially specific  
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37 133 binding function in short term memory, and that this function appears to be  
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39 134 independent of PHC's role in recall precision.  
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3 136 **Methods**

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5 137 PJ: history and clinical assessment

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7 138 PJ was first seen by one of the authors (CR), four months after he had suffered a  
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9 139 cerebrovascular accident. PJ was 45 years old when he developed headaches, visual  
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11 140 and mental status changes over the course of a few hours. Two days after the onset of  
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13 141 these symptoms, he was admitted to a stroke-unit at a regional hospital. During the  
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15 142 admission, he continued to be confused and agitated. The diagnostic work-up revealed  
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17 143 bilateral posterior circulation strokes involving the occipito-temporal cortex. No cause  
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19 144 for the stroke was identified. PJ had no significant medical history, except for  
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21 145 cluster headaches, which responded well to standard treatment.  
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27 147 Upon returning home, he was not able to resume his full-time occupation as an animal  
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29 148 breeder, because of difficulties finding his way around the house and farm, where he  
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31 149 had moved two years prior. He also relinquished driving, because he could not find  
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33 150 his way around familiar streets. He was able to sketch the overall layout of his home,  
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35 151 but frequently misidentified rooms and the family resorted to placing signs on internal  
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37 152 doors to help him find his way around. His ability to repair equipment around the  
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39 153 farm was also diminished, because of difficulty identifying the correct tool in a  
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41 154 cluttered environment.  
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47 156 PJ's visual perimetry was formally assessed three and five months following the  
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49 157 ischemic injury, with a binocular field test (Esterman, 1982). He showed strict upper  
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51 158 quadrantanopias, worse on the left than on the right. There was evidence of partial  
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53 159 recovery on the second assessment (see figure S3).  
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3 161 Formal clinical psychometric testing was conducted approximately 6 months  
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5 162 following his stroke. The standardised scores are presented in table 1. His general  
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7 163 intellectual functioning fell within the average range, as measured with the Wechsler  
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9 164 Adult Intelligence scale, fourth edition (WAIS-IV). This was affected negatively by  
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11 165 slowed processing speed on visual tasks. He performed similarly on the verbal  
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13 166 (Verbal Comprehension Index) and non-verbal scale (Perceptual Reasoning Index) of  
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15 167 the WAIS-IV. His expressive and receptive language functions were grossly intact.  
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17 168 He did however often require verbal instructions to be repeated. His information-  
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19 169 processing speed was in the borderline range on the WAIS-IV. Memory function was  
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21 170 significantly impaired for both visual and verbal material. He had difficulties with  
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23 171 learning and acquisition of new material and also with delayed recall. Performance  
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25 172 was not improved for recognition memory. His errors on a visual memory task were  
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27 173 primarily misplacement errors. He demonstrated set-loss errors on a word generation  
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29 174 task and also required reminding of rules on a problem-solving task. Performance on  
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31 175 executive functioning tasks was mixed; he performed at the expected level on a  
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33 176 planning and problem-solving task. His performance on a verbal fluency task was  
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35 177 within normal limits. His score on an attention-shifting and inhibition task was in the  
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37 178 impaired range of ability. PJ passed on all subtests of object perception from the  
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39 179 Visual Object and Space Perception Battery (Warrington and James 1991), except for  
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41 180 progressive silhouettes, where he had a raw score of 11, indicating mild impairment.  
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43 181 He was also faultless in all subtests of space perception.  
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52 183 PJ was scanned using a research MRI protocol and tested behaviourally at the Bangor  
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54 184 University School of Psychology approximately one year and ten months following  
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56 185 the ischemic event, when he was 47 years of age. Testing took place on two  
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3 186 consecutive days.  
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7 188 Control Participants  
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10 189 *Behavioural comparison:* Ten right-handed, healthy male participants were recruited  
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12 190 from the local community. Controls were screened for any history of major  
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14 191 neuropsychiatric disorders and visual impairments. IQ was measured with the 2-  
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16 192 subtest (vocabulary and matrix reasoning) version of the Wechsler Abbreviated Scale  
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18 193 of Intelligence (WASI; Wechsler 1999). Table 2 summarises the characteristics of the  
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20 194 control group. The mean age was 48.2 years (sd: 6.4), the mean IQ was 101.1 (sd:  
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22 195 7.6) and the mean age leaving school was 16.6 (sd: 0.7). On all these variables, PJ and  
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24 196 controls were matched; all p-values were above .095 using a modified t-test  
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26 197 (Crawford and Howell 1998).  
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32 199 *Anatomical comparison:* A convenience sample of 10 healthy male participants was  
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34 200 drawn from a Bangor University image register. The mean age was 43.3 years (sd:  
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36 201 4.9).  
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40 203 All participants were compensated for their time and travel expenses. All participants  
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42 204 gave written, informed consent prior to initiating any experimental procedure. The  
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44 205 testing procedures had been reviewed and approved by the Betsi Cadwaladr  
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46 206 University Health Board and the Bangor University School Psychology Ethics  
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48 207 committees.  
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52 209 Behavioural testing: overview and material  
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3 210 PJ and controls performed three computer-based behavioural experiments. Testing  
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5 211 took place in a dark room; participants sat comfortably, unrestrained, approximately  
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7 212 85cm from an LCD screen (NEC LCD3210). Participants were encouraged to actively  
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9 213 scan the display and foveate individual stimuli. Custom-coded Matlab scripts  
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11 214 (Mathworks 2014a), using a set of freely available routines designed to facilitate the  
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13 215 coding of visual experiments (Brainard 1997), controlled the experiments and  
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15 216 generated the displays. Matlab scripts were run on an Apple iMac 10.  
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### 20 21 218 Statistical comparison of PJ and controls

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23 219 We computed the significance of performance differences between PJ and the control  
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25 220 group in all experiments using a modified t-test (Crawford and Howell 1998). Where  
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27 221 performance was measured with a percentage or ratio, we conducted the t-test on  
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29 222 logarithmically transformed values.  
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## 35 **Imaging**

### 36 225 Imaging – image acquisition and analysis

37  
38 226 PJ and the anatomical comparison controls were scanned on a Phillips Achieva 3T  
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40 227 MR scanner with a 32-channel head coil. T1 weighted images (TE = 4.32ms; 8° flip  
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42 228 angle) were acquired axially with a 0.7mm isotropic voxel-size. PJ's T1 weighted  
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44 229 anatomical volume was bias corrected and normalised to the atlas representative  
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46 230 MNI152 template using SPM12 (Ashburner and Friston 2003). The mapping included  
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48 231 a 12-degrees-of-freedom affine transform followed by a local deformation, computed  
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50 232 after the lesion had been masked using a hand-drawn region. The normalised anatomy  
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52 233 was obtained by interpolation via a 4<sup>th</sup> degree B-spline, and resampled using a 0.7mm  
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54 234 linear voxel size. Skull stripped anatomy was obtained using a modified version of  
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3 235 FSL's BET, which is optimised for tissue segmentation in the presence of brain  
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5 236 pathology (Lutkenhoff et al. 2014). To determine whether PJ's stroke encroached  
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7 237 onto perirhinal and entorhinal cortex, probabilistic maps of these regions were  
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9 238 superimposed on his brain anatomy (Hindy and Turk-Browne 2016). Lesion  
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11 239 boundaries were drawn by a board-certified adult neurologist, using the co-registered  
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14 240 T1 and FLAIR images.

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18 242 Lesion anatomy results

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21 243 Figure 1 shows axial and coronal slices from the MNI Atlas co-registered T1-  
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23 244 weighted scan of PJ's brain. In the left hemisphere the lesion volume is 6.25 cm<sup>3</sup>, in  
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25 245 the right hemisphere 10.71 cm<sup>3</sup>. Figure 1A shows that the ischemic lesions in medial  
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27 246 occipitotemporal cortex (mOTC) of the left and right hemisphere lie posterior to the  
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29 247 location of entorhinal and perirhinal cortex (marked respectively in red and green),  
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31 248 identified in a previous group study (Hindy and Turk-Browne 2016). Figure S1  
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33 249 provides additional anatomical information about the relationship between lesion and  
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35 250 entorhinal and perirhinal cortex. The coronal slices in figure 1B demonstrate that the  
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37 251 fornix is intact, however sections -23 to -32 suggest hippocampal volume loss on the  
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39 252 right. Also, retrosplenial cortex and the adjacent precuneus are spared in both  
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41 253 hemispheres. Figure S2 shows sagittal slices through medial brain structures, which  
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43 254 highlights the extent of the damage to PHC and lingual gyrus. Given the apparent  
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45 255 hippocampal volume loss, we compared PJ's left and right hippocampal volumes to  
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47 256 those of the anatomical comparison controls. A stereological procedure was used to  
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49 257 estimate hippocampal volumes in all participants (Keller and Roberts 2009). The  
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51 258 input images were the T1 weighted brain volumes in native scanner space. A regular  
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53 259 cubic grid with a step of 3 pixels was superimposed on coronal slices, with a random  
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3 260 starting position. The senior author, a board-certified neurologist, outlined the  
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5 261 hippocampal formation to determine the number of overlaying grid points. The  
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7 262 hippocampal formation included the hippocampus, dentate gyrus and subiculum. The  
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10 263 anterior border of the hippocampal formation was the alveus, the posterior border was  
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12 264 the crux of the fornix. The hippocampal borders were also identified in axial and  
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14 265 sagittal slices. The procedure was implemented using ImageJ (Schneider et al. 2012)  
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16 266 and a stereology dedicated plugin (Merzin 2008). This analysis indicated that PJ's left  
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18 267 ( $3931\text{mm}^3$ ) and right ( $2530\text{mm}^3$ ) hippocampi were not significantly smaller than  
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20 268 controls (left: mean =  $3561\text{mm}^3$ ;  $t(9) = 0.516$ ,  $p = 0.618$ ; right: mean =  $3816\text{mm}^3$   $t(9)$   
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22 269 =  $-1.79$ ,  $p = 0.108$ ). However, the volumetric difference between the left and right  
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24 270 hippocampi was significantly greater for PJ than for controls ( $t(9) = 2.641$ ,  $p = 0.027$ ),  
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26 271 suggesting that PJ's right hippocampus may have been atrophied.  
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### 31 32 **Experiment 1: spatial vs. non-spatial binding in working memory**

#### 33 34 Experiment 1 – Rationale

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36 275 Primate studies (Malkova and Mishkin 2003; Belcher et al. 2006) have suggested that  
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38 276 PHC is involved in remembering locations in close peri-personal space as well as  
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40 277 spatial binding in working memory. In this first experiment, we examined visual  
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42 278 working memory spatial and feature binding in PJ, a man with PHC lesions, and a  
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44 279 group of age-matched controls. On each trial, participants had to remember the  
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46 280 colour, shape and location of two objects. After a short delay, participants were cued  
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48 281 to recall the colour of one of the objects, identified either by its location on the screen,  
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50 282 or by its shape. We reasoned that if human PHC is involved in spatial binding, then  
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52 283 PJ's recall performance should be worse than controls, specifically on location trials.  
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3 285 Experiment 1 – Methods  
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5 286 Figure 2A shows a schematic representation of Experiment 1's trial structure. In each  
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7 287 trial, an equilateral triangle and a square, whose side lengths were  $2.42^\circ$  and  $1.72^\circ$   
8  
9 288 respectively, appeared side-to-side in the lower half of the screen, at an eccentricity of  
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11 289  $4.25^\circ$  along the main diagonal, for 2.0s. The shapes were either red, blue or green. A  
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13 290 200ms pattern mask, and then a 2.0s blank screen, followed the sample display. The  
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15 291 recall screen contained three coloured rectangles,  $1.0^\circ$  wide and  $3.0^\circ$  high, whose  
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17 292 lower edges were aligned  $2.5^\circ$  above the screen center and spaced horizontally  $9.0^\circ$   
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19 293 apart. A bright cross (location cue) or the outline of one of the two shapes (shape cue)  
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21 294 identified the target. The location cues, which also included a dark cross, appeared at  
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23 295 the locations occupied by the two shapes. The shape cue appeared  $3.0^\circ$  below the  
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25 296 screen center. Participants reported the target colour by placing a cursor over the  
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27 297 corresponding coloured rectangle and clicking the mouse button. The mouse click  
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29 298 prompted the beginning of a new trial, after a 1.0s delay, during which the screen was  
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31 299 blank. Participants practiced the task over ten trials and then completed ninety trials,  
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33 300 including both shape and location cued recalls. Trial order was randomised,  
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35 301 minimising participants' ability to predict whether a shape or location cue would  
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37 302 follow the sample display. To ensure that PJ had not forgotten the task instructions,  
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39 303 we asked him to describe what he had been doing after each block. In each instance  
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41 304 he correctly reported that he had been recalling either the probed shape colour, or the  
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43 305 colour at the location of the white cross.  
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51 307 Experiment 1 – Data analysis  
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54 308 We scored trials based on whether participants reported (a) the correct target colour  
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56 309 (correct response), (b) the colour of the non-target shape (binding error), or (c) neither  
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3 310 the target nor the non-target colour, i.e., dummy colour (generic error). We then  
4  
5 311 calculated the proportion of binding (BE) and generic errors (GE) for each cue  
6  
7 312 condition (location and shape) and compared PJ and the control group's recall accuracy  
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9  
10 313 using odds ratios. We computed two odds ratios: the first was the ratio of the  
11  
12 314 proportion of binding errors in location vs. shape cued trials (i.e.,  $[BE_{\text{location}} / BE_{\text{shape}}]$ ).  
13  
14 315 The second was the ratio of binding errors over generic errors in location vs. shape  
15  
16 316 cued trials (i.e.,  $[BE_{\text{location}} / GE_{\text{location}}] / [BE_{\text{shape}} / GE_{\text{shape}}]$ ). If a participant's data cells  
17  
18 317 contained zero counts, a value of 0.5 was added to all cells prior to computing the  
19  
20  
21 318 ratios (Gart and Zweifel 1967).  
22

23 319

#### 24 320 Experiment 1 – Results: impaired spatial binding in visual working memory

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26  
27 321 The left-hand panels of figures 2B and 2C report the proportion of generic errors  
28  
29 322 following location and shape cues, while the right-hand panels show the proportion of  
30  
31 323 binding errors. PJ made more binding errors when the target was identified by a  
32  
33 324 location than a shape cue ( $p < 0.001$ ; Fisher exact test). PJ was also much more likely  
34  
35 325 to make a binding than a generic error following a location ( $p < 0.001$ , two-tailed  
36  
37 326 binomial test), but not a shape cue ( $p = 0.5$ ), suggesting that his difficulties did not  
38  
39 327 reflect a problem remembering which colours had been shown. For PJ, the odds ratio  
40  
41 328 of making a binding error in the location vs. shape cue trials was 60.7, which was  
42  
43 329 significantly greater than the control group average of 0.501 (95% CI: [0.23 - 1.06],  
44  
45 330  $t(9) = 3.72$ ,  $p = 0.005$ ), suggesting that he was much more likely to make a binding  
46  
47 331 error on location than shape cue trials, while controls were modestly more accurate  
48  
49 332 following a location than a shape cue. Moreover, PJ's odds ratio of making a binding  
50  
51 333 rather than a generic error in the location vs shape cued trials was 29.0 which was  
52  
53 334 again significantly greater than the control group average of 0.421 (95% CI: [0.21 -  
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3 335 0.83],  $t(9) = 3.46$ ,  $p = 0.007$ ), confirming that he was much more likely to make a  
4  
5 336 binding than a generic error on location rather than shape cued trials, while controls  
6  
7 337 were more likely to make a binding than a generic error on shape rather than location  
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9 338 trials.

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14 340 Experiment 1: Interim discussion

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16 341 PJ showed a remarkable deficit binding objects to their location in a working memory  
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18 342 task. When he reported the colour of one of two objects, he was able to do so  
19  
20 343 accurately for targets cued by their shape. However, when a target was identified by  
21  
22 344 its location, his performance was greatly diminished because of numerous binding  
23  
24 345 errors. Control participants, on the other hand, showed comparable recall accuracy  
25  
26 346 irrespective of the cue type. These findings strongly suggest that PJ's impairment  
27  
28 347 cannot be attributed to either diminished memory for the report feature, i.e. the  
29  
30 348 target's colour, or a binding deficit that generalises across visual dimensions. Rather,  
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32 349 PJ shows a binding impairment that is specifically spatial.

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**Experiment 2: delayed spatial recall**

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41 352 Experiment 2 – Rationale

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43 353 In the previous experiment, we demonstrated that PJ suffers a specific spatial binding  
44  
45 354 impairment in a working memory task. In experiment 2, we examined whether spatial  
46  
47 355 binding impairments reflect diminished resolution of spatial data in working memory,  
48  
49 356 or rather disruption of spatial binding. To this end we assessed the effects of the  
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51 357 duration of the memory delay on both the precision of spatial recall and the  
52  
53 358 proportion of binding errors.

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## 360 Experiment 2 – Methods

361 Figure 3A summarises Experiment 2's trial structure. The sample stimulus consisted  
362 of three coloured discs,  $0.8^\circ$  in diameter. The discs were red, green and blue, and  
363 remained visible for 2.0s. A 1.0s long pattern mask followed the sample. A central  
364 colour cue (a  $0.3^\circ$  wide square) appeared either immediately after the pattern mask, or  
365 after an additional 4.0s interval, during which only a white central fixation point was  
366 visible. The cue identified the target of the same colour. The participants placed the  
367 cursor at the recalled target location and clicked the mouse to record their response  
368 and initiate the next trial. The location of the discs included the center of the screen  
369 and the vertices of a virtual square, at an eccentricity of  $6.0^\circ$ . 2D Gaussian  
370 displacement (s.d. =  $0.9^\circ$ ) jittered the position of each disc. Each participant completed  
371 two blocks of one hundred and twenty trials each.

372

## 373 Experiment 2 – Data analysis

374 First, we identified trials in which participants had made a binding error, i.e. when the  
375 recalled position was closer to the one of the non-target items than the target, and the  
376 distance from the non-target item was no greater than half the minimum distance  
377 between canonical locations, i.e.  $3.0^\circ$  (Pertzov et al. 2013). After tabulating and  
378 removing binding errors, we estimated recall accuracy and precision. Accuracy  
379 reflects how close a participant's average reported location is to the true target  
380 position. Precision reflects the magnitude of trial-to-trial deviations from a  
381 participant's average reported location. Accuracy is diminished by systematic errors,  
382 which depend on factors such as display size and memory load (Katshu and d'Avossa  
383 2014), while precision is thought to reflect the resolution of spatial memory (Bays et  
384 al. 2009). These two variables were computed using linear regressions. We computed

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2  
3 385 two regressions whose dependent variables were the azimuth and elevation of the  
4  
5 386 reported target location, respectively. The regressors in each case included a constant  
6  
7 387 and the target's azimuth and elevation. The results of the regression analysis were  
8  
9 388 used to estimate the systematic biases reporting the target location. The scaling factor  
10  
11 389 was the divergence of the error field, which we previously found to be the main linear  
12  
13 390 component of the systematic error (Katshu and d'Avossa 2014). We quantified recall  
14  
15 391 precision using the standard deviation of the residuals from the model fits. The  
16  
17 392 variance and standard deviations of the variable errors were computed using the same  
18  
19 393 procedure employed in a previous study (Katshu and d'Avossa 2014), and averaged  
20  
21 394 over azimuth and elevation. Precision changes between short and long delays were  
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23 395 quantified using an efficiency measure, namely a ratio whose numerator was the  
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25 396 recall variance following 1.0s delays and denominator was recall variance following  
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27 397 5.0s delays.  
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34 399 Experiment 2 – Results: recall precision, but not binding errors, affected by memory  
35  
36 400 delay  
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38 401 PJ made more binding errors than controls, following both 1.0s and 5.0s delays.  
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40 402 Otherwise, both PJ and controls performed similarly in terms of accuracy and  
41  
42 403 precision.  
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47 405 The proportion of binding errors are shown in the left-hand panels of figure 3B and  
48  
49 406 3C. Overall, PJ made a binding error on 9.44% of trials, which was significantly  
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51 407 greater than the control group average of 3.21% (95% CI: [2.24 - 4.18];  $t(9) = 4.02$ ;  $p$   
52  
53 408 = 0.003). Increasing the duration of the memory delay had no effect on the proportion  
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55 409 of PJ's relative binding errors; PJ's odds ratio for making a binding error following  
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3 410 1.0s vs. 5.0s delays was 1.27, which was not significantly different to the control  
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5 411 group average of 1.0 (95% CI: [0.72 - 1.38];  $t(9) = 0.462$ ;  $p = 0.655$ ), and suggested a  
6  
7 412 non-significant tendency for more binding errors following short than long memory  
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10 413 delays. Further, 40% (6/15) of PJ's binding errors on short delay trials, and 50%  
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12 414 (6/12) of his binding errors on long delay trials, occurred when the target appeared in  
13  
14 415 the upper portion of the screen; a goodness of fit test reported that his binding errors  
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16 416 were not biased toward the target appearing in either the upper or lower half of the  
17  
18 417 screen following either delay ( $\chi^2(3) = 1$ ,  $p = .801$ ). We can therefore conclude that his  
19  
20 418 binding issues are unlikely due to his upper visual field deficit impacting the encoding  
21  
22 419 of the entire sample stimulus.  
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27 421 Both PJ and controls showed systematic distortions. Following both short and long  
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29 422 memory delays, PJ reported targets displaced leftward (1.0s:  $-0.24^\circ$ ; 5.0s:  $-0.23^\circ$ ) and  
30  
31 423 upward (1.0s:  $0.15^\circ$ ; 5.0s:  $0.09^\circ$ ). In contrast, controls' group mean displacement was  
32  
33 424 rightward (1.0s:  $0.09^\circ$ , 95% CI: [-0.09 - 0.26]; 5.0s:  $0.07^\circ$ , 95% CI: [-0.12 - 0.27];)  
34  
35 425 and downward (1.0s:  $-0.37^\circ$ , 95% CI: [-0.55 - -0.19]; 5.0s:  $-0.28^\circ$ , 95% CI: [-0.45 - -  
36  
37 426  $0.11$ ]). However, PJ's displacements were not significantly different from controls for  
38  
39 427 both delays (all  $p$ -values  $> 0.100$ ). PJ also tended to overestimate the position of  
40  
41 428 targets relative to the screen center, indicated by an error divergence of 0.04 following  
42  
43 429 1.0s delays and 0.16 following 5.0s delays. In contrast, controls underestimated  
44  
45 430 targets relative to the screen center, as indicated by a group average error divergence  
46  
47 431 of  $-0.26$  (95% CI: [-0.36 - -0.15]) following 1.0s delays and  $-0.29$  (95% CI: [-0.41 - -  
48  
49 432  $0.16$ ]) following 5.0s delays. However, PJ and controls did not differ significantly  
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51 433 (both  $p$ -values  $> 0.055$ ).  
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3 435 Recall precision data are summarised in the right-hand panel of figure 3B and 3C. In  
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5 436 contrast to binding errors, increasing the delay had a significant effect on recall  
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7 437 precision. PJ's error standard deviation was  $1.33^\circ$  following 1.0s delays, which was  
8  
9 438 not statistically different from the control group average of  $1.01^\circ$  (95% CI: [0.91 –  
10  
11 439 1.10];  $t(9) = 2.11$ ;  $p = 0.064$ ). PJ's error standard deviation following 5.0s delays  
12  
13 440 ( $1.78^\circ$ ) was statistically larger than the control group average of  $1.18^\circ$  (95% CI: [1.09  
14  
15 441 – 1.27];  $t(9) = 4.23$ ;  $p = 0.002$ ). However, PJ's efficiency after a 5.0s delay compared  
16  
17 442 to a 1.0s delay was 0.56, which was not significantly smaller than the control group  
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19 443 average of 0.73 (95% CI: [0.65 – 0.82];  $t(9) = -1.37$ ;  $p = 0.203$ ).  
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#### 24 25 445 Experiment 2: Interim discussion

26  
27 446 The experiment yielded a number of findings. First PJ made more binding errors than  
28  
29 447 controls, confirming that he exhibited an impairment of spatial binding using a task in  
30  
31 448 which the target location was the report rather than the cue variable. Secondly,  
32  
33 449 following 1.0s delay the precision recalling the target location was not appreciably  
34  
35 450 different between PJ and controls, suggesting that his binding impairment did not  
36  
37 451 reflect a problem recalling the target location precisely. Moreover, while increasing  
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39 452 the memory delay did not increase the proportion of binding errors, it did significantly  
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41 453 diminish both PJ and controls' spatial recall precision, providing additional evidence  
42  
43 454 that recall precision did not account for binding errors. In summary, PJ shows  
44  
45 455 frequent binding errors, but spatial recall precision which is comparable to that of  
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47 456 controls. Crucially, changing the duration of the memory delay produces dissociable  
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49 457 effects on recall precision and binding.  
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#### 55 56 459 **Experiment 3: centroid estimation**

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3 460 Experiment 3 – Rationale  
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5 461 In experiment 3 we ascertained whether PJ's diminished recall of a target position  
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7 462 may reflect a sensory impairment. While this seems unlikely given the finding that  
8  
9 463 PJ's recall precision was not significantly diminished compared to controls (with 1.0s  
10  
11 464 delay), it was important to establish the extent to which sensory difficulties may have  
12  
13 465 limited his performance. We therefore assessed participants' spatial accuracy and  
14  
15 466 precision in a perceptual task.  
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21 468 Experiment 3 – Methods  
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23 469 This experiment assessed participants' ability to localise the centroid, namely the  
24  
25 470 average location, of three white discs. The discs' diameter was  $0.5^\circ$  (see figure 4A for  
26  
27 471 a schematic representation of the trial structure). The discs remained visible until  
28  
29 472 participants had positioned a crosshair shaped cursor at the desired location and  
30  
31 473 clicked the mouse. Following a blank, 1.0s-long interval, a novel set of discs appeared  
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33 474 and the procedure was repeated. Discs could occupy any of seven canonical locations.  
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35 475 These included the screen center and the vertices of a virtual concentric hexagon, with  
36  
37 476 a side length of  $6.87^\circ$ . All permutations of three out of seven canonical target  
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39 477 locations, less any resulting in a collinear configuration, were used as sample arrays.  
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41 478 Each possible permutation appeared twice, for a total of sixty-four trials. A  
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43 479 pseudorandom, zero mean, circular Gaussian distribution, with a standard deviation of  
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45 480  $0.6^\circ$ , was used to jitter each disc's position independently. Prior to testing,  
46  
47 481 instructions were read to the participants. The centroid was defined as the point in  
48  
49 482 space where the triangle, whose vertices coincided with the discs' locations, would  
50  
51 483 balance in the horizontal plane (Baud-Bovy and Soechting 2001). One of the  
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53 484 experimenters also provided a visual demonstration, using a cut-out triangular shape.  
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3 485 Prior to testing, participants completed twenty-five practice trials. At the end of each  
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5 486 practice trial, the reported and actual positions of the centroid were shown for 2.0s.  
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10 488 Experiment 3 – Data analysis

11 489 We estimated the systematic and variable error of participants' centroid estimations,  
12  
13 490 by fitting a linear model to the azimuth and elevation of the reported centroid  
14  
15 491 location. The model regressors included a constant and the centroid azimuth and  
16  
17 492 elevation. Two metrics were used to characterise the systematic error: 1) the constant  
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19 493 displacement, that is the tendency to report the centroid above, below, right or left of  
20  
21 494 its true location, and 2) scaling factor, measuring the linear relationship between  
22  
23 495 reported and actual centroid positions. These are, respectively, the estimated intercept  
24  
25 496 and beta parameters of the linear model. We computed precision as the standard  
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27 497 deviation of the variable error, i.e., residuals from the model, using the same methods  
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29 498 used in Experiment 2.  
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35  
36 500 Experiment 3 – Results: accuracy and precision of centroid estimation

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38 501 The left-hand panels of figure 4B and 4C illustrate the direction of systematic biases  
39  
40 502 in centroid estimates. PJ and controls respectively reported the centroid  $-0.07^\circ$  and -  
41  
42 503  $0.10^\circ$  (95% CI:  $[-0.15^\circ - -0.04^\circ]$ ) left of its veridical position, suggesting that both  
43  
44 504 showed a similarly small leftward bias, ( $t(9) = 0.322$ ,  $p = 0.755$ ). However, PJ  
45  
46 505 reported the centroid  $0.56^\circ$  above its veridical position. This bias was significantly  
47  
48 506 larger than controls, who showed a group average upward bias of  $0.06^\circ$  (95% CI:  $[-$   
49  
50 507  $0.02^\circ - 0.14^\circ]$ ;  $t(9) = 3.69$ ,  $p = 0.005$ ). The middle panel of figure 4B and 4C  
51  
52 508 summarise the linear scaling for centroid estimates. PJ varied the reported centroid  
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54 509 azimuth by a factor of 0.97, and elevation by a factor of 1.00, in both cases reflecting  
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3 510 an almost perfect linear relationship between reported and actual centroid positions.  
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5 511 These values were comparable to those shown by controls, namely 0.99 for azimuth  
6  
7 512 (95% CI: [0.94 – 1.03];  $t(9) = -0.263$ ,  $p = 0.799$ ), and 0.97 for elevation (95%CI:  
8  
9 513 [0.93 – 1.01];  $t(9) = 0.443$ ,  $p = 0.668$ ). Finally, PJ's azimuth variable error standard  
10  
11 514 deviation,  $0.67^\circ$ , was not significantly different from the control average of  $0.69^\circ$   
12  
13 515 (95%CI = [ $0.56^\circ - 0.82^\circ$ ];  $t(9) = -0.091$ ,  $p = 0.931$ ), nor was his elevation variable  
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15 516 error standard deviation,  $0.77^\circ$ , significantly different from the control average of  
16  
17 517  $0.59^\circ$  (95%CI = [ $0.47^\circ - 0.70^\circ$ ];  $t(9) = 0.925$ ,  $p = 0.380$ ), suggesting that both the  
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19 518 vertical and horizontal precision of his centroid judgements was relatively spared.  
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### 25 520 Experiment 3 – Interim discussion

26  
27 521 PJ showed a strong tendency to report the centroid above its true location. This  
28  
29 522 probably represents a compensatory strategy for his upper visual field defect. In fact,  
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31 523 hemianopic patients display a bias toward their blind field when judging the midpoint  
32  
33 524 of horizontal line (Barton and Black 1998; Kerkhoff and Buchers 2008). However,  
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35 525 both PJs accuracy and precision estimating the centroid position were within the  
36  
37 526 control group's range. We conclude that aside from compensatory visual defect  
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39 527 biases, PJ's ability to localise perceptually is largely spared and unlikely to account  
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41 528 for his diminished recall precision.  
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3 530**Discussion**

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5 531 We tested a middle-aged man (PJ) with bilateral mOTC strokes involving the PHC.  
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7 532 Acutely, PJ had developed a derangement of attention and short-term memory  
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9 533 (Horenstein et al. 1967; Medina et al. 1977; Shih et al. 2007). At the time of testing,  
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11 534 PJ was no longer delirious, but continued to have difficulties with his memory as well  
12  
13 535 as navigating familiar environments. The latter is a form of spatial disorientation  
14  
15 536 previously attributed to PHC lesions in humans (Zola-Morgan et al. 1989; Epstein et  
16  
17 537 al. 2001). Animal studies have demonstrated additional deficits in spatial working  
18  
19 538 memory following PHC lesions in non-human primates (Malkova and Mishkin 2003;  
20  
21 539 Bachevalier and Nemanic 2008). Whether the same deficits characterise human  
22  
23 540 patients with PHC lesions is not yet known.  
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28 541

29 542 We found that PJ had a profound deficit binding an object to its location in a working  
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31 543 memory task. When he recalled the colour of one of two objects, after a short memory  
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33 544 delay, he could accurately do so when the target was cued by its shape. However,  
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35 545 when the target was cued by its location, his accuracy was greatly diminished because  
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37 546 he made numerous binding errors, frequently reporting the colour of the non-target  
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39 547 item instead of the colour of the target. Control participants, on the other hand, were  
40  
41 548 accurate whether the target was identified by the location or shape cue. These findings  
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43 549 strongly suggest that PJ was impaired only when using a location cue and that this  
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45 550 impairment could not be attributed to either diminished memory for the report feature,  
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47 551 i.e. the target's colour, or a binding deficit that generalises across spatial and non-  
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49 552 spatial visual dimensions. According to a recent study, generalised binding difficulties  
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51 553 may instead characterise recall performance in individuals with autoimmune temporal  
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53 554 encephalitis, which mainly affects the hippocampal formation (Pertzov et al. 2013).  
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5 556 Some animal and imaging studies have indeed shown that both anterior PHC and  
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7 557 hippocampus contribute to object-in-place associations in short-term memory (Milner  
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9 558 et al. 1997; Bachevalier and Nemanic 2008). However, animal data suggest that  
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11 559 hippocampal involvement in spatial binding is restricted to tasks where spatial  
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13 560 relations are incidentally encoded (Bachevalier and Nemanic 2008). These findings,  
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15 561 together with ours, suggest that in tasks where spatial information is intentionally  
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17 562 encoded and recalled, the role of PHC goes beyond simply providing spatial data to  
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19 563 the hippocampus, where general purpose processes bind visual features in working  
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21 564 memory. Moreover, our findings confirm that binding in visual working memory is  
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23 565 liable to be disrupted by focal brain lesions (Gorgoraptis et al. 2011), supporting the  
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25 566 idea that it is a neural function independent from those underpinning the  
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27 567 representations of individual features (Wheeler and Treisman 2002; Smyrnis et al.  
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29 568 2005).

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36 570 Binding errors do not reflect the resolution of spatial information

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38 571 When PJ reported the location of one of three objects held in memory he erroneously  
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40 572 reported the location of one of the non-target items more frequently than controls.  
41  
42 573 This finding suggests that PJ had difficulties with spatial binding, whether space was  
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44 574 the cue or report dimension. One might argue that PJ's spatial binding impairment  
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46 575 simply reflects degraded spatial representations. In other words, diminished ability  
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48 576 recalling the location of an object might explain his difficulties using spatial  
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50 577 information to identify targets in memory. However, this hypothesis is not supported  
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52 578 by our data. PJ was able to estimate the centroid of simple dot configurations as  
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54 579 precisely as controls, indicating that despite the presence of an upper visual field  
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3 580 defect, the spatial resolution of visual data was not prominently affected in this  
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5 581 perceptual task. Moreover, PJ's precision recalling the location of visual targets was  
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7 582 not appreciably different from that of controls, even though his proportion of spatial  
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9 583 binding errors was much greater. Finally, binding errors did not become more  
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11 584 frequent when the delay interval was increased, although the precision of spatial recall  
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13 585 did decrease. We conclude that binding errors do not reflect the temporal decay of a  
14  
15 586 memory trace, contrary to previous suggestions (Zhang and Luck 2009). Moreover,  
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17 587 our findings are consistent with observations that binding errors are not affected by  
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19 588 the duration of the memory delay in either patients with hippocampal pathology  
20  
21 589 (Pertzov et al. 2013) or healthy controls (Gorgoraptis et al. 2011), although whether  
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23 590 binding errors may be effected by longer (e.g., >20.0s) delays remains to be  
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25 591 established. Finally, varying the spatial memory demands at the time of recall in a  
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27 592 spatial version of the Sternberg working memory task does not change the likelihood  
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29 593 of committing a binding error, confirming that binding errors do not reflect confusion  
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31 594 among features of the probe dimension (Smyrnis et al. 2005). Taken together, the  
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33 595 available evidence in healthy controls and patients instead suggests that binding errors  
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35 596 reflect interference with early processes, engaged at the time when visual information  
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37 597 is encoded in working memory. However, a recent high-resolution fMRI study has  
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39 598 suggested that load dependent signals in PHC during the delay period of a match-to-  
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41 599 sample-task may reflect on-going binding processes (Schon et al. 2016).  
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#### 601 Delays affect the precision of spatial recall

602 PJ's spatial recall precision was similar to that of controls when the memory delay  
603 lasted 1.0s. When the memory delay was 5.0s long, both he and controls suffered a  
604 decrement in recall precision. These are not entirely novel findings. Recall precision

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3 605 is known to decrease with longer memory delays in healthy controls (Sheth and  
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5 606 Shimojo 2001; Zhang and Luck 2009). Moreover, recall precision disproportionately  
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7 607 decreases in patients with PHC lesions, although significantly so only following  
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9 608 memory delays greater than 20s (Ploner et al. 2000). This finding is in keeping with  
10  
11 609 our own: recall efficiency following 5.0s vs 1.0s delays was lower in PJ than in  
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13 610 controls, however this difference was not significant. Combined, these data are  
14  
15 611 consistent with the idea that following PHC lesions, spatial recall precision decays  
16  
17 612 more quickly than in healthy controls, as opposed to declining abruptly. More  
18  
19 613 generally, our findings are in keeping with the view that spatial recall draws  
20  
21 614 information from a limited capacity resource (Bays et al. 2009), whose resolution  
22  
23 615 diminishes over time. Therefore, delay dependent changes in spatial recall precision  
24  
25 616 most likely reflect a limited ability to maintain information in working memory rather  
26  
27 617 than impaired encoding, in contrast to the binding deficits discussed above. Finally,  
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29 618 PJ's performance in our experiments is consistent with his neuropsychological profile,  
30  
31 619 which is principally characterised by impairment on various memory tasks, including  
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33 620 those that do not have a spatial binding component, such as the Logical Memory test  
34  
35 621 and the Rey Auditory Verbal Learning Test. However we do not yet know the extent  
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37 622 to which diminished recall precision and spatial binding account for the broad  
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39 623 memory deficits observed following lesions to PHC.  
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625 Could the hippocampus be the site for short term memory spatial binding?

626 In the present study we identified impairments resulting from focal lesions to PHC,  
627 and found a spatial binding deficit in short term memory. Our data cannot rule out the  
628 possibility that binding takes place outside PHC, for example, in the hippocampus.  
629 Indeed, comparison of hippocampal volumes in PJ and age and gender matched

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3 630 controls suggest hippocampal atrophy in PJ. Lateralised hippocampal atrophy  
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5 631 commonly follows distal, ipsilateral stroke, even in young patients unlikely to harbour  
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7 632 neurodegenerative processes (Schaapsmeeders et al. 2015a, 2015b), suggesting that  
8  
9 633 the hippocampus may be particularly vulnerable to the effects of deafferentation. Pj's  
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11 634 hippocampal atrophy raises the possibility that spatial binding deficits reflect  
12  
13 635 diminished function within the hippocampus. Our data cannot refute this alternative  
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15 636 hypothesis. As mentioned in the introduction, previous studies in patients with  
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17 637 inflammatory and anoxic damage involving the hippocampus (e.g. Pertzov et al.  
18  
19 638 2013; Watson et al. 2013; Yee et al. 2014) have also demonstrated spatial binding  
20  
21 639 impairments, lending support to the hippocampus' role in feature binding.  
22  
23 640 Nonetheless, the specific spatial nature of PJ's binding impairment, which did not  
24  
25 641 generalise to other visual dimensions (i.e., shape), is inconsistent with the proposal  
26  
27 642 that the hippocampus provides a general purpose binding mechanism. Therefore, we  
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29 643 conclude that spatial binding is either carried out in hippocampus, using inputs from  
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31 644 PHC, or that PHC itself initiates spatial binding processes.  
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#### 646 Concluding remarks

41 647 This study provides novel information on the role of MTL, by showing that a man  
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43 648 with a lesion involving PHC, hippocampal atrophy, but spared PRC, has a selective  
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45 649 deficit in short term spatial binding. This deficit is not explained by diminished  
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47 650 resolution of spatial information. Our findings are consistent with the idea that spatial  
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49 651 binding processes in short term memory may be initiated in the PHC even before  
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51 652 visual information reaches the hippocampus.  
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For Peer Review

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**Tables**

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Neurocognitive domain / Test / Subtest	Raw score	Standard/Z Score	Percentile
<b>Intellectual Functioning</b>			
<i>Wechsler Intelligence Scale - IV</i>			
Full Scale IQ		87	19
Verbal Comprehension Index		96	39
Perceptual Reasoning Index		90	25
Working Memory Index		92	25
Processing Speed Index		79	8
Vocabulary		9	37
Similarities		9	37
Information		10	50
Block Design		9	37
Matrix Reasoning		5	5
Visual Puzzles		11	63
Digit Span		9	37
Arithmetic		8	25
Symbol Search		7	16
Coding		5	5
<b>Learning and Memory</b>			
<i>Wechsler Memory Scale</i>			
Logical Memory I	11/75	2	0.4
Logical Memory II	4/50	3	1
Visual Reproduction I	56	4	2



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2				
3	Visual Reproduction II	13	5	5
4				
5	<i>Auditory Verbal Learning Test</i>			
6				
7	Trial I	3	-2	2
8				
9	Trial II	4	-2.33	1
10				
11	Trial III	5	-2	2
12				
13	Trial IV	8	-1.15	13
14				
15	Trial V	5	-3.31	1
16				
17	List B	4	-1.11	13
18				
19	Trial VI	3	-2.2	2
20				
21	Delayed Recall	1	-2.54	1
22				
23	Recognition	1	-4.3	1
24				
25				
26				
27	<i>Rey Complex Figure Test</i>			
28				
29	Copy	36	1.38	92
30				
31	30 minute recall	1.5	-2.25	< 1
32				
33				
34	<i>Benton Visual Retention Test</i>			
35				
36	Correct score	3	-2.69	< 1
37				
38	Error score	13	-3.35	< 1
39				
40				
41				
42	<b>Attention/Executive Function</b>			
43				
44	<i>Trail Making Test</i>			
45				
46	Part A	72 sec	-4.05	< 1
47				
48		131		
49	Part B		-4.66	< 1
50		sec		
51				
52				
53	<i>D-K Executive Function System</i>			
54				
55	Verbal Fluency Test			
56				
57				
58				
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Letter Fluency	25	6	9
Category Fluency	39	10	50
<i>Tower Test</i>			
Total Achievement Score	16	10	50
<i>Stroop Test</i>			
Colour task	112		
Colour-word task	38		> 2

### Object recognition and Space

#### Perception

##### *The Visual Object and Space Perception*

##### *Battery*

##### *Object Perception*

Screening Test	20/20 (Pass)
Incomplete Letters	19/20 (Pass)
Silhouettes	19/30 (Pass)
Object Decision	17/20 (Pass)
Progressive Silhouettes	11 (Fail)

##### *Space Perception*

Dot Counting	10/10 (Pass)
Position Discrimination	20/20 (Pass)
Number Location	10/10 (Pass)
Cube Analysis	10/10 (Pass)

910

911 *Table 1. Summary of PJ's neuropsychometric performance six months after stroke.*

912

Gender	Handed	Age	IQ	Age Leaving School
M	Right	51	106	18
M	Right	43	111	16
M	Right	45	99	16
M	Right	61	103	17
M	Right	39	109	18
M	Right	47	90	16
M	Right	53	88	16
M	Right	46	104	17
M	Right	53	97	16
M	Right	44	104	16
	<b>Mean</b>	48.2	101.1	16.6
	<b>SD</b>	6.4	7.6	0.8

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*Table 2. Control group demographics and IQ*

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**Captions**

926  
927 Figure 1. Lesion anatomy. T1 weighted, MNI atlas registered axial (panel A) and  
928 coronal (panel B) slices are displayed in neurological coordinates, and illustrate the  
929 extent of ischemic damage in the left and right mOTC. In panel A, the axial slices  
930 also highlight the location of entorhinal and perirhinal cortex, in red and green  
931 respectively. These regions lay anteriorly and laterally to the boundaries of the  
932 ischemic lesions. In panel B, coronal slices highlight parahippocampal and  
933 hippocampal structures, including the fornix. The ischemic lesions lay inferiorly and  
934 posteriorly to the hippocampus and spare the fornix and the retrosplenial cingulate  
935 cortex.

936  
937 Figure 2. Spatial vs. non-spatial binding in working memory. Panel A shows the trial  
938 structure. The sample display for all participants (including PJ) contained a square  
939 and a triangle, placed side by side in the bottom half of the screen. The two objects  
940 were red, blue or green and never had the same colour. After a brief pattern mask and  
941 blank delay, three vertical coloured bars appeared as well as a cursor, which the  
942 participant used to report the colour of the memory target. In shape trials, targets were  
943 identified by a probe whose outline matched the target shape. In location trials, the  
944 location of targets were identified by a white cross. Panel B shows each individual  
945 participants' error rate on a greyscale, with lighter colours representing a higher  
946 proportion of errors; the left panel shows generic errors, the right panel shows binding  
947 errors. On each panel, the upper row shows errors following shape probes, while the  
948 lower row shows errors following location probes, for PJ (blue outline) and each of  
949 the controls (red outline). Panel C shows PJ's and the group averaged proportion of  
950 generic and binding errors. Error bars are standard error of the mean.

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3 951  
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5 952 Figure 3. Delayed spatial recall. Panel A shows the structure of immediate and  
6  
7 953 delayed, spatial recall trials. The sample display for all participants (including PJ)  
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10 954 contained three coloured discs, which could appear in both the upper and lower  
11  
12 955 portion of the screen. The participants had to reproduce the position of one of the  
13  
14 956 discs (the target) using a mouse cursor after either a 1.0s pattern mask or an additional  
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16 957 4.0s delay. The target was identified by its colour, indicated by a visual probe  
17  
18 958 displayed at the center of the screen. Panel B (left) shows PJ's (blue outline) and  
19  
20 959 controls' (red outline) individual percentage of binding errors on a greyscale,  
21  
22 960 following 1.0s (upper row) and 5.0s (lower row) delays, with lighter colours  
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24 961 representing a higher proportion of errors. Panel B (right) shows recall precision (95%  
25  
26 962 error ellipses) in 1.0s and 5.0s delayed recall trials for PJ (blue) and controls (red).  
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28 963 Panel C shows PJ's and the group averaged proportion of binding errors and  
29  
30 964 precision. Error bars are standard error of the mean.  
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36 966 Figure 4. Centroid estimation. Panel A shows the trial structure. The participants  
37  
38 967 placed a cursor at the centroid of the configuration formed by three bright discs. The  
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40 968 discs remained visible until the participant made a response by clicking the mouse.  
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43 969 Panel B shows each participant's constant displacement (arrow vectors), scaling  
44  
45 970 (diamond plot) and precision (uncertainty ellipses) in locating the centroid. The length  
46  
47 971 of the diamond plot's hemi-axes corresponds to 1.0 scaling factor. Panel C shows PJ's  
48  
49 972 and group averaged values of the constant displacement and scaling factor, separately  
50  
51 973 for azimuth (X) and elevation (Y). The precision measure shown is the square root of  
52  
53 974 the mean error variance for azimuth and elevation. Error bars in all cases are standard  
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55 975 error of the mean.  
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For Peer Review

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3 **1 Human parahippocampal cortex supports spatial binding in visual working**  
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5 **2 memory**  
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25 **Running title:** Human PHC supports spatial binding

1  
2  
3 26 **Abstract**

4  
5 27 Studies investigating the functional organisation of the medial temporal lobe (MTL)  
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7 28 suggest that parahippocampal cortex (PHC) generates representations of spatial and  
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10 29 contextual information used by the hippocampus in the formation of episodic  
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12 30 memories. However, evidence from animal studies also implicates PHC in spatial  
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14 31 binding of visual information held in short term, working memory. Here we examined  
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16 32 a 46-year-old man (PJ), after he had recovered from bilateral medial occipitotemporal  
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18 33 cortex strokes resulting in ischemic lesions of PHC and hippocampal atrophy, and a  
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21 34 group of age-matched healthy controls. When recalling the colour of one of two  
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23 35 objects, PJ misidentified the target when cued by its location, but not shape. When  
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25 36 recalling the position of one of three objects, he frequently misidentified the target,  
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27 37 which was cued by its colour. Increasing the duration of the memory delay had no  
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29 38 impact on the proportion of binding errors, but did significantly worsen recall  
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31 39 precision in both PJ and controls. We conclude that PHC may play a crucial role in  
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34 40 spatial binding during encoding of visual information in working memory.

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37 41  
38 42 **Keywords:** Feature binding; Medial temporal lobe; Parahippocampal cortex; Spatial  
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40 43 Memory; Visual working memory

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## 44 Introduction

45 The medial temporal lobe (MTL) comprises the hippocampus and parahippocampal  
46 regions, i.e., entorhinal cortex, perirhinal cortex (PRC) and parahippocampal cortex  
47 (PHC). These structures play a prominent role in episodic memory, as evidenced by  
48 the dense anterograde amnesia, which follows damage to MTL (Scoville and Milner  
49 1957; Corkin 1984; Corkin et al. 1997). Modular accounts of MTL function have  
50 suggested that the hippocampus synthesises episodic memories by binding  
51 information about the identity and location of objects carried respectively by two  
52 different streams (Eichenbaum et al. 2007; Diana et al. 2007).

53  
54 MTL structures have also been implicated in short term memory processes  
55 (Ranganath and Blumenfeld 2005; Graham et al. 2010; Yonelinas, 2013). First,  
56 animal models have pointed to specific molecular mechanisms in the mammalian  
57 MTL dedicated to the storage of short term memories, and separate from those  
58 involved in long term memory (Deacon et al. 2002; Reisel et al. 2002). Single unit  
59 recordings and lesion studies in non-human primates have further demonstrated that  
60 the hippocampus (Friedman and Goldman-Rakic 1988), entorhinal cortex (Suzuki et  
61 al. 1997), PRC (Davachi and Goldman-Rakic 2001) and PHC (Bachevalier and  
62 Nemanic 2008) contribute to the encoding and recall of information from short term  
63 memory. These animal findings complement neuropsychological studies of patients  
64 with amnesia resulting from Korsakoff's Syndrome, encephalitis and colloid cysts  
65 (Holdstock et al. 1995), and patients with surgical (Aggleton 1992; Owen et al. 1995)  
66 or ischemic (Holdstock et al. 2002) lesions to the MTL, demonstrating retention  
67 deficits for novel stimuli over delay intervals as short as two seconds (Ranganath  
68 and Blumenfeld 2005).

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70 An increasing body of evidence further suggests that short term memory exploits the  
71 same MTL modules as episodic memory; that is, PRC codes information about an  
72 object's identity and PHC codes an object's location and its context, and these two  
73 streams are bound in the hippocampus (Pertzov et al. 2013; Watson et al. 2013; Yee et  
74 al. 2014; Libby et al. 2014). Consistent with the idea that in short term memory  
75 identity and location information are processed separately and then bound, patients  
76 with hippocampal damage can exhibit deficits recalling object-location conjunctions  
77 after 1.0s delays, even when unimpaired recalling either object identities or locations  
78 (Olson et al. 2006a; 2006b). However, other studies report that patients with damage  
79 to the hippocampus do not necessarily show deficits in recalling object-location  
80 conjunctions, suggesting that spatial binding is preserved (e.g. Jenson et al. 2010; see  
81 Yonelinas 2013 for a review).

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83 An alternative possibility is that spatial binding in short term memory occurs in  
84 parahippocampal regions, rather than the hippocampus proper. In support of this  
85 view, data in both rats (Burwell and Amaral 1998) and monkeys (Suzuki and Amaral  
86 1994) indicate that PRC and PHC are reciprocally connected, suggesting that the  
87 parcellation of identity and spatial information is not absolute, and that there may  
88 already be substantial cross-talk between object and spatial/context related  
89 information in parahippocampal regions. Further, recordings in rats have  
90 demonstrated single unit responses for object-location conjunctions in the PHC  
91 homologue (Barker and Warburton 2011).

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3 93 Behavioural studies in monkeys have provided crucial evidence for the role of PHC in  
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5 94 spatial binding. Rhesus monkeys with PHC lesions are impaired in both simple  
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7 95 location and object-location conjunction tasks (Malkova and Mishkin, 2003). This  
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10 96 short term memory impairment was observed in a delayed match-to-sample task,  
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12 97 where the sample contained two non-identical objects. After a six-second delay, the  
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14 98 test array contained one of the objects in its original location (the target), and an  
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16 99 identical item either at the location of the sample foil (object-place condition), or at a  
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18 100 novel location not previously occupied by either sample object (location condition).  
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21 101 Monkeys with PHC lesions were impaired identifying the target in both conditions,  
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23 102 while monkeys with lesions in the hippocampus showed no impairment in either task  
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25 103 (Malkova and Mishkin 2003). Hippocampectomised monkeys were likewise  
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27 104 unimpaired in a later study, using a more difficult task with an increased number of  
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29 105 objects and locations (Belcher et al. 2006).  
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34 107 A cross-species homology in the short term memory functionality of PHC is partly  
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36 108 supported by the observation that patients with PHC lesions also exhibit a decrement  
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38 109 in spatial recall (Ploner et al. 2000), although this impairment is only observed using  
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40 110 delays greater (i.e. >15.0s) than those used by Malkova and Mishkin (2003). In  
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42 111 addition, functional imaging data in healthy subjects demonstrate heightened right  
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44 112 PHC activation during both encoding and maintenance of object-location  
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46 113 conjunctions, relative to trials where objects or locations are memorised separately  
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48 114 (Luck et al. 2010). However, no neuropsychological study has so far demonstrated  
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50 115 that PHC contributes to spatial binding in human short term memory.  
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3 117 In the present study, we examined the nature and extent of spatial and short term  
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5 118 memory deficits associated with focal PHC lesions, by testing a middle-aged man (PJ)  
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7 119 with bilateral posterior circulation strokes involving the PHC, but sparing the  
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9 120 hippocampus and PRC. Our experiments were driven by three specific research  
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11 121 questions: 1) does damage to PHC produce binding difficulties and if so, are the  
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13 122 binding problems specifically spatial or do they generalise to other visual dimensions;  
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15 123 2) do binding impairments reflect deficits in memory encoding or maintenance; and  
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17 124 3) is the binding impairment secondary to a loss of positional information either in  
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19 125 memory or perception?  
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25 127 Both PJ and controls showed dependent decrements in the precision of spatial recall,  
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27 128 however PJ's recall precision was significantly worse than controls at longer delays  
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29 129 (5.0s). PJ also showed impaired spatial binding. This impairment was unaffected by  
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31 130 the duration of the memory delay. Finally, PJ's binding deficits did not generalise  
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33 131 across visual dimensions, since he performed normally when recall involved the  
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35 132 conjunction of non-spatial features. We conclude that PHC serves a spatially specific  
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37 133 binding function in short term memory, and that this function appears to be  
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39 134 independent of PHC's role in recall precision.  
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3 136 **Methods**

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5 137 PJ: history and clinical assessment

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7 138 PJ was first seen by one of the authors (CR), four months after he had suffered a  
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10 139 cerebrovascular accident. PJ was 45 years old when he developed headaches, visual  
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12 140 and mental status changes over the course of a few hours. Two days after the onset of  
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14 141 these symptoms, he was admitted to a stroke-unit at a regional hospital. During the  
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16 142 admission, he continued to be confused and agitated. The diagnostic work-up revealed  
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18 143 bilateral posterior circulation strokes involving the occipito-temporal cortex. No cause  
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20 144 for the stroke was identified. PJ had no significant medical history, except for  
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22 145 cluster headaches, which responded well to standard treatment.  
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27 147 Upon returning home, he was not able to resume his full-time occupation as an animal  
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29 148 breeder, because of difficulties finding his way around the house and farm, where he  
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31 149 had moved two years prior. He also relinquished driving, because he could not find  
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33 150 his way around familiar streets. He was able to sketch the overall layout of his home,  
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35 151 but frequently misidentified rooms and the family resorted to placing signs on internal  
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37 152 doors to help him find his way around. His ability to repair equipment around the  
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39 153 farm was also diminished, because of difficulty identifying the correct tool in a  
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41 154 cluttered environment.  
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47 156 PJ's visual perimetry was formally assessed three and five months following the  
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49 157 ischemic injury, with a binocular field test (Esterman, 1982). He showed strict upper  
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51 158 quadrantanopias, worse on the left than on the right. There was evidence of partial  
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53 159 recovery on the second assessment (see figure S3).  
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3 161 Formal clinical psychometric testing was conducted approximately 6 months  
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5 162 following his stroke. The standardised scores are presented in table 1. His general  
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7 163 intellectual functioning fell within the average range, as measured with the Wechsler  
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9 164 Adult Intelligence scale, fourth edition (WAIS-IV). This was affected negatively by  
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11 165 slowed processing speed on visual tasks. He performed similarly on the verbal  
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13 166 (Verbal Comprehension Index) and non-verbal scale (Perceptual Reasoning Index) of  
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15 167 the WAIS-IV. His expressive and receptive language functions were grossly intact.  
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17 168 He did however often require verbal instructions to be repeated. His information-  
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19 169 processing speed was in the borderline range on the WAIS-IV. Memory function was  
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21 170 significantly impaired for both visual and verbal material. He had difficulties with  
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23 171 learning and acquisition of new material and also with delayed recall. Performance  
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25 172 was not improved for recognition memory. His errors on a visual memory task were  
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27 173 primarily misplacement errors. He demonstrated set-loss errors on a word generation  
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29 174 task and also required reminding of rules on a problem-solving task. Performance on  
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31 175 executive functioning tasks was mixed; he performed at the expected level on a  
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33 176 planning and problem-solving task. His performance on a verbal fluency task was  
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35 177 within normal limits. His score on an attention-shifting and inhibition task was in the  
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37 178 impaired range of ability. PJ passed on all subtests of object perception from the  
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39 179 Visual Object and Space Perception Battery (Warrington and James 1991), except for  
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41 180 progressive silhouettes, where he had a raw score of 11, indicating mild impairment.  
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43 181 He was also faultless in all subtests of space perception.  
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52 183 PJ was scanned using a research MRI protocol and tested behaviourally at the Bangor  
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54 184 University School of Psychology approximately one year and ten months following  
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56 185 the ischemic event, when he was 47 years of age. Testing took place on two  
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3 186 consecutive days.  
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7 188 Control Participants

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10 189 *Behavioural comparison:* Ten right-handed, healthy male participants were recruited  
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12 190 from the local community. Controls were screened for any history of major  
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14 191 neuropsychiatric disorders and visual impairments. IQ was measured with the 2-  
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16 192 subtest (vocabulary and matrix reasoning) version of the Wechsler Abbreviated Scale  
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18 193 of Intelligence (WASI; Wechsler 1999). Table 2 summarises the characteristics of the  
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20 194 control group. The mean age was 48.2 years (sd: 6.4), the mean IQ was 101.1 (sd:  
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22 195 7.6) and the mean age leaving school was 16.6 (sd: 0.7). On all these variables, PJ and  
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24 196 controls were matched; all p-values were above .095 using a modified t-test  
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26 197 (Crawford and Howell 1998).  
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32 199 *Anatomical comparison:* A convenience sample of 10 healthy male participants was  
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34 200 drawn from a Bangor University image register. The mean age was 43.3 years (sd:  
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36 201 4.9).  
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40 203 All participants were compensated for their time and travel expenses. All participants  
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42 204 gave written, informed consent prior to initiating any experimental procedure. The  
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44 205 testing procedures had been reviewed and approved by the Betsi Cadwaladr  
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46 206 University Health Board and the Bangor University School Psychology Ethics  
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48 207 committees.  
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52 209 Behavioural testing: overview and material  
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3 210 PJ and controls performed three computer-based behavioural experiments. Testing  
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5 211 took place in a dark room; participants sat comfortably, unrestrained, approximately  
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7 212 85cm from an LCD screen (NEC LCD3210). Participants were encouraged to actively  
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9 213 scan the display and foveate individual stimuli. Custom-coded Matlab scripts  
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11 214 (Mathworks 2014a), using a set of freely available routines designed to facilitate the  
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13 215 coding of visual experiments (Brainard 1997), controlled the experiments and  
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15 216 generated the displays. Matlab scripts were run on an Apple iMac 10.  
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### 20 21 218 Statistical comparison of PJ and controls

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23 219 We computed the significance of performance differences between PJ and the control  
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25 220 group in all experiments using a modified t-test (Crawford and Howell 1998). Where  
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27 221 performance was measured with a percentage or ratio, we conducted the t-test on  
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29 222 logarithmically transformed values.  
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## 35 **Imaging**

### 36 225 Imaging – image acquisition and analysis

37  
38 226 **PJ and the anatomical comparison controls were** scanned on a Phillips Achieva 3T  
39  
40 227 MR scanner with a 32-channel head coil. T1 weighted images (TE = 4.32ms; 8° flip  
41  
42 228 angle) were acquired axially with a 0.7mm isotropic voxel-size. **PJ's** T1 weighted  
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44 229 anatomical volume was bias corrected and normalised to the atlas representative  
45  
46 230 MNI152 template using SPM12 (Ashburner and Friston 2003). **The mapping included**  
47  
48 231 **a 12-degrees-of-freedom affine transform followed by a local deformation, computed**  
49  
50 232 **after the lesion had been masked using a hand-drawn region. The normalised anatomy**  
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52 233 **was obtained by interpolation via a 4<sup>th</sup> degree B-spline, and resampled using a 0.7mm**  
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54 234 **linear voxel size.** Skull stripped anatomy was obtained using a modified version of  
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3 235 FSL's BET, which is optimised for tissue segmentation in the presence of brain  
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5 236 pathology (Lutkenhoff et al. 2014). To determine whether PJ's stroke encroached  
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7 237 onto perirhinal and entorhinal cortex, probabilistic maps of these regions were  
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9 238 superimposed on his brain anatomy (Hindy and Turk-Browne 2016). Lesion  
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11 239 boundaries were drawn by a board-certified adult neurologist, using the co-registered  
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13 240 T1 and FLAIR images.

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18 242 Lesion anatomy results

19  
20 243 Figure 1 shows axial and coronal slices from the MNI Atlas co-registered T1-  
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22 244 weighted scan of PJ's brain. In the left hemisphere the lesion volume is 6.25 cm<sup>3</sup>, in  
23  
24 245 the right hemisphere 10.71 cm<sup>3</sup>. Figure 1A shows that the ischemic lesions in medial  
25  
26 246 occipitotemporal cortex (mOTC) of the left and right hemisphere lie posterior to the  
27  
28 247 location of entorhinal and perirhinal cortex (marked respectively in red and green),  
29  
30 248 identified in a previous group study (Hindy and Turk-Browne 2016). Figure S1  
31  
32 249 provides additional anatomical information about the relationship between lesion and  
33  
34 250 entorhinal and perirhinal cortex. The coronal slices in figure 1B demonstrate that the  
35  
36 251 fornix is intact, however sections -23 to -32 suggest hippocampal volume loss on the  
37  
38 252 right. Also, retrosplenial cortex and the adjacent precuneus are spared in both  
39  
40 253 hemispheres. Figure S2 shows sagittal slices through medial brain structures, which  
41  
42 254 highlights the extent of the damage to PHC and lingual gyrus. Given the apparent  
43  
44 255 hippocampal volume loss, we compared PJ's left and right hippocampal volumes to  
45  
46 256 those of the anatomical comparison controls. A stereological procedure was used to  
47  
48 257 estimate hippocampal volumes in all participants (Keller and Roberts 2009). The  
49  
50 258 input images were the T1 weighted brain volumes in native scanner space. A regular  
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52 259 cubic grid with a step of 3 pixels was superimposed on coronal slices, with a random  
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3 260 starting position. The senior author, a board-certified neurologist, outlined the  
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5 261 hippocampal formation to determine the number of overlaying grid points. The  
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7 262 hippocampal formation included the hippocampus, dentate gyrus and subiculum. The  
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10 263 anterior border of the hippocampal formation was the alveus, the posterior border was  
11  
12 264 the crux of the fornix. The hippocampal borders were also identified in axial and  
13  
14 265 sagittal slices. The procedure was implemented using ImageJ (Schneider et al. 2012)  
15  
16 266 and a stereology dedicated plugin (Merzin 2008). This analysis indicated that PJ's left  
17  
18 267 ( $3931\text{mm}^3$ ) and right ( $2530\text{mm}^3$ ) hippocampi were not significantly smaller than  
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21 268 controls (left: mean =  $3561\text{mm}^3$ ;  $t(9) = 0.516$ ,  $p = 0.618$ ; right: mean =  $3816\text{mm}^3$   $t(9)$   
22  
23 269 =  $-1.79$ ,  $p = 0.108$ ). However, the volumetric difference between the left and right  
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25 270 hippocampi was significantly greater for PJ than for controls ( $t(9) = 2.641$ ,  $p = 0.027$ ),  
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27 271 suggesting that PJ's right hippocampus may have been atrophied.  
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### 272 32 **Experiment 1: spatial vs. non-spatial binding in working memory**

#### 33 34 Experiment 1 – Rationale

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36 275 Primate studies (Malkova and Mishkin 2003; Belcher et al. 2006) have suggested that  
37  
38 276 PHC is involved in remembering locations in close peri-personal space as well as  
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41 277 spatial binding in working memory. In this first experiment, we examined visual  
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43 278 working memory spatial and feature binding in PJ, a man with PHC lesions, and a  
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45 279 group of age-matched controls. On each trial, participants had to remember the  
46  
47 280 colour, shape and location of two objects. After a short delay, participants were cued  
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49 281 to recall the colour of one of the objects, identified either by its location on the screen,  
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51  
52 282 or by its shape. We reasoned that if human PHC is involved in spatial binding, then  
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54 283 PJ's recall performance should be worse than controls, specifically on location trials.  
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3 285 Experiment 1 – Methods  
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5 286 Figure 2A shows a schematic representation of Experiment 1's trial structure. In each  
6  
7 287 trial, an equilateral triangle and a square, whose side lengths were  $2.42^\circ$  and  $1.72^\circ$   
8  
9 288 respectively, appeared side-to-side in the lower half of the screen, at an eccentricity of  
10  
11 289  $4.25^\circ$  along the main diagonal, for 2.0s. The shapes were either red, blue or green. A  
12  
13 290 200ms pattern mask, and then a 2.0s blank screen, followed the sample display. The  
14  
15 291 recall screen contained three coloured rectangles,  $1.0^\circ$  wide and  $3.0^\circ$  high, whose  
16  
17 292 lower edges were aligned  $2.5^\circ$  above the screen center and spaced horizontally  $9.0^\circ$   
18  
19 293 apart. A bright cross (location cue) or the outline of one of the two shapes (shape cue)  
20  
21 294 identified the target. The location cues, which also included a dark cross, appeared at  
22  
23 295 the locations occupied by the two shapes. The shape cue appeared  $3.0^\circ$  below the  
24  
25 296 screen center. Participants reported the target colour by placing a cursor over the  
26  
27 297 corresponding coloured rectangle and clicking the mouse button. The mouse click  
28  
29 298 prompted the beginning of a new trial, after a 1.0s delay, during which the screen was  
30  
31 299 blank. Participants practiced the task over ten trials and then completed ninety trials,  
32  
33 300 including both shape and location cued recalls. Trial order was randomised,  
34  
35 301 minimising participants' ability to predict whether a shape or location cue would  
36  
37 302 follow the sample display. To ensure that PJ had not forgotten the task instructions,  
38  
39 303 we asked him to describe what he had been doing after each block. In each instance  
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41 304 he correctly reported that he had been recalling either the probed shape colour, or the  
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43 305 colour at the location of the white cross.  
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52 307 Experiment 1 – Data analysis  
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54 308 We scored trials based on whether participants reported (a) the correct target colour  
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56 309 (correct response), (b) the colour of the non-target shape (binding error), or (c) neither  
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3 310 the target nor the non-target colour, i.e., dummy colour (generic error). We then  
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5 311 calculated the proportion of binding (BE) and generic errors (GE) for each cue  
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7 312 condition (location and shape) and compared PJ and the control group's recall accuracy  
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9  
10 313 using odds ratios. We computed two odds ratios: the first was the ratio of the  
11  
12 314 proportion of binding errors in location vs. shape cued trials (i.e.,  $[BE_{\text{location}} / BE_{\text{shape}}]$ ).  
13  
14 315 The second was the ratio of binding errors over generic errors in location vs. shape  
15  
16 316 cued trials (i.e.,  $[BE_{\text{location}} / GE_{\text{location}}] / [BE_{\text{shape}} / GE_{\text{shape}}]$ ). If a participant's data cells  
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18 317 contained zero counts, a value of 0.5 was added to all cells prior to computing the  
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20  
21 318 ratios (Gart and Zweifel 1967).  
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23 319

24  
25 320 Experiment 1 – Results: impaired spatial binding in visual working memory  
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27 321 The left-hand panels of figures 2B and 2C report the proportion of generic errors  
28  
29 322 following location and shape cues, while the right-hand panels show the proportion of  
30  
31 323 binding errors. PJ made more binding errors when the target was identified by a  
32  
33 324 location than a shape cue ( $p < 0.001$ ; Fisher exact test). PJ was also much more likely  
34  
35 325 to make a binding than a generic error following a location ( $p < 0.001$ , two-tailed  
36  
37 326 binomial test), but not a shape cue ( $p = 0.5$ ), suggesting that his difficulties did not  
38  
39 327 reflect a problem remembering which colours had been shown. For PJ, the odds ratio  
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41 328 of making a binding error in the location vs. shape cue trials was 60.7, which was  
42  
43 329 significantly greater than the control group average of 0.501 (95% CI: [0.23 - 1.06],  
44  
45 330  $t(9) = 3.72$ ,  $p = 0.005$ ), suggesting that he was much more likely to make a binding  
46  
47 331 error on location than shape cue trials, while controls were modestly more accurate  
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49 332 following a location than a shape cue. Moreover, PJ's odds ratio of making a binding  
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51 333 rather than a generic error in the location vs shape cued trials was 29.0 which was  
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53 334 again significantly greater than the control group average of 0.421 (95% CI: [0.21 -  
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3 335 0.83],  $t(9) = 3.46$ ,  $p = 0.007$ ), confirming that he was much more likely to make a  
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5 336 binding than a generic error on location rather than shape cued trials, while controls  
6  
7 337 were more likely to make a binding than a generic error on shape rather than location  
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9 338 trials.  
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#### 14 340 Experiment 1: Interim discussion

16 341 PJ showed a remarkable deficit binding objects to their location in a working memory  
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18 342 task. When he reported the colour of one of two objects, he was able to do so  
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20 343 accurately for targets cued by their shape. However, when a target was identified by  
21  
22 344 its location, his performance was greatly diminished because of numerous binding  
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24 345 errors. Control participants, on the other hand, showed comparable recall accuracy  
25  
26 346 irrespective of the cue type. These findings strongly suggest that PJ's impairment  
27  
28 347 cannot be attributed to either diminished memory for the report feature, i.e. the  
29  
30 348 target's colour, or a binding deficit that generalises across visual dimensions. Rather,  
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32 349 PJ shows a binding impairment that is specifically spatial.  
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#### 351 **Experiment 2: delayed spatial recall**

#### 352 Experiment 2 – Rationale

353 In the previous experiment, we demonstrated that PJ suffers a specific spatial binding  
354  
354 354 impairment in a working memory task. In experiment 2, we examined whether spatial  
355  
355 355 binding impairments reflect diminished resolution of spatial data in working memory,  
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356 356 or rather disruption of spatial binding. To this end we assessed the effects of the  
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357 357 duration of the memory delay on both the precision of spatial recall and the  
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358 358 proportion of binding errors.  
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### 360 Experiment 2 – Methods

361 Figure 3A summarises Experiment 2's trial structure. The sample stimulus consisted  
362 of three coloured discs,  $0.8^\circ$  in diameter. The discs were red, green and blue, and  
363 remained visible for 2.0s. A 1.0s long pattern mask followed the sample. A central  
364 colour cue (a  $0.3^\circ$  wide square) appeared either immediately after the pattern mask, or  
365 after an additional 4.0s interval, during which only a white central fixation point was  
366 visible. The cue identified the target of the same colour. The participants placed the  
367 cursor at the recalled target location and clicked the mouse to record their response  
368 and initiate the next trial. The location of the discs included the center of the screen  
369 and the vertices of a virtual square, at an eccentricity of  $6.0^\circ$ . 2D Gaussian  
370 displacement (s.d. =  $0.9^\circ$ ) jittered the position of each disc. Each participant completed  
371 two blocks of one hundred and twenty trials each.

372

### 373 Experiment 2 – Data analysis

374 First, we identified trials in which participants had made a binding error, i.e. when the  
375 recalled position was closer to the one of the non-target items than the target, and the  
376 distance from the non-target item was no greater than half the minimum distance  
377 between canonical locations, i.e.  $3.0^\circ$  (Pertzov et al. 2013). After tabulating and  
378 removing binding errors, we estimated recall accuracy and precision. Accuracy  
379 reflects how close a participant's average reported location is to the true target  
380 position. Precision reflects the magnitude of trial-to-trial deviations from a  
381 participant's average reported location. Accuracy is diminished by systematic errors,  
382 which depend on factors such as display size and memory load (Katshu and d'Avossa  
383 2014), while precision is thought to reflect the resolution of spatial memory (Bays et  
384 al. 2009). These two variables were computed using linear regressions. We computed

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3 385 two regressions whose dependent variables were the azimuth and elevation of the  
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5 386 reported target location, respectively. The regressors in each case included a constant  
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7 387 and the target's azimuth and elevation. The results of the regression analysis were  
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9 388 used to estimate the systematic biases reporting the target location. The scaling factor  
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11 389 was the divergence of the error field, which we previously found to be the main linear  
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13 390 component of the systematic error (Katshu and d'Avossa 2014). We quantified recall  
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15 391 precision using the standard deviation of the residuals from the model fits. The  
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17 392 variance and standard deviations of the variable errors were computed using the same  
18  
19 393 procedure employed in a previous study (Katshu and d'Avossa 2014), and averaged  
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21 394 over azimuth and elevation. Precision changes between short and long delays were  
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23 395 quantified using an efficiency measure, namely a ratio whose numerator was the  
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25 396 recall variance following 1.0s delays and denominator was recall variance following  
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27 397 5.0s delays.  
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34 399 Experiment 2 – Results: recall precision, but not binding errors, affected by memory  
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36 400 delay

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38 401 PJ made more binding errors than controls, following both 1.0s and 5.0s delays.  
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40 402 Otherwise, both PJ and controls performed similarly in terms of accuracy and  
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42 403 precision.  
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47 405 The proportion of binding errors are shown in the left-hand panels of figure 3B and  
48  
49 406 3C. Overall, PJ made a binding error on 9.44% of trials, which was significantly  
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51 407 greater than the control group average of 3.21% (95% CI: [2.24 - 4.18];  $t(9) = 4.02$ ;  $p$   
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53 408 = 0.003). Increasing the duration of the memory delay had no effect on the proportion  
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55 409 of PJ's relative binding errors; PJ's odds ratio for making a binding error following  
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3 410 1.0s vs. 5.0s delays was 1.27, which was not significantly different to the control  
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5 411 group average of 1.0 (95% CI: [0.72 - 1.38];  $t(9) = 0.462$ ;  $p = 0.655$ ), and suggested a  
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7 412 non-significant tendency for more binding errors following short than long memory  
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9 413 delays. Further, 40% (6/15) of PJ's binding errors on short delay trials, and 50%  
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11 414 (6/12) of his binding errors on long delay trials, occurred when the target appeared in  
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13 415 the upper portion of the screen; a goodness of fit test reported that his binding errors  
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15 416 were not biased toward the target appearing in either the upper or lower half of the  
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17 417 screen following either delay ( $\chi^2(3) = 1$ ,  $p = .801$ ). We can therefore conclude that his  
18  
19 418 binding issues are unlikely due to his upper visual field deficit impacting the encoding  
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21 419 of the entire sample stimulus.  
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27 420  
28 421 Both PJ and controls showed systematic distortions. Following both short and long  
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30 422 memory delays, PJ reported targets displaced leftward (1.0s:  $-0.24^\circ$ ; 5.0s:  $-0.23^\circ$ ) and  
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32 423 upward (1.0s:  $0.15^\circ$ ; 5.0s:  $0.09^\circ$ ). In contrast, controls' group mean displacement was  
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34 424 rightward (1.0s:  $0.09^\circ$ , 95% CI: [-0.09 - 0.26]; 5.0s:  $0.07^\circ$ , 95% CI: [-0.12 - 0.27];)  
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36 425 and downward (1.0s:  $-0.37^\circ$ , 95% CI: [-0.55 - -0.19]; 5.0s:  $-0.28^\circ$ , 95% CI: [-0.45 - -  
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38 426  $0.11$ ]). However, PJ's displacements were not significantly different from controls for  
39  
40 427 both delays (all  $p$ -values  $> 0.100$ ). PJ also tended to overestimate the position of  
41  
42 428 targets relative to the screen center, indicated by an error divergence of 0.04 following  
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44 429 1.0s delays and 0.16 following 5.0s delays. In contrast, controls underestimated  
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46 430 targets relative to the screen center, as indicated by a group average error divergence  
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48 431 of  $-0.26$  (95% CI: [-0.36 - -0.15]) following 1.0s delays and  $-0.29$  (95% CI: [-0.41 - -  
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50 432  $0.16$ ]) following 5.0s delays. However, PJ and controls did not differ significantly  
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52 433 (both  $p$ -values  $> 0.055$ ).  
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3 435 Recall precision data are summarised in the right-hand panel of figure 3B and 3C. In  
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5 436 contrast to binding errors, increasing the delay had a significant effect on recall  
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7 437 precision. PJ's error standard deviation was  $1.33^\circ$  following 1.0s delays, which was  
8  
9 438 not statistically different from the control group average of  $1.01^\circ$  (95% CI: [0.91 –  
10  
11 439 1.10];  $t(9) = 2.11$ ;  $p = 0.064$ ). PJ's error standard deviation following 5.0s delays  
12  
13 440 ( $1.78^\circ$ ) was statistically larger than the control group average of  $1.18^\circ$  (95% CI: [1.09  
14  
15 441 – 1.27];  $t(9) = 4.23$ ;  $p = 0.002$ ). However, PJ's efficiency after a 5.0s delay compared  
16  
17 442 to a 1.0s delay was 0.56, which was not significantly smaller than the control group  
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19 443 average of 0.73 (95% CI: [0.65 – 0.82];  $t(9) = -1.37$ ;  $p = 0.203$ ).  
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#### 25 445 Experiment 2: Interim discussion

26  
27 446 The experiment yielded a number of findings. First PJ made more binding errors than  
28  
29 447 controls, confirming that he exhibited an impairment of spatial binding using a task in  
30  
31 448 which the target location was the report rather than the cue variable. Secondly,  
32  
33 449 following 1.0s delay the precision recalling the target location was not appreciably  
34  
35 450 different between PJ and controls, suggesting that his binding impairment did not  
36  
37 451 reflect a problem recalling the target location precisely. Moreover, while increasing  
38  
39 452 the memory delay did not increase the proportion of binding errors, it did significantly  
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41 453 diminish both PJ and controls' spatial recall precision, providing additional evidence  
42  
43 454 that recall precision did not account for binding errors. In summary, PJ shows  
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45 455 frequent binding errors, but spatial recall precision which is comparable to that of  
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47 456 controls. Crucially, changing the duration of the memory delay produces dissociable  
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49 457 effects on recall precision and binding.  
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#### 56 459 **Experiment 3: centroid estimation**

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3 460 Experiment 3 – Rationale  
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5 461 In experiment 3 we ascertained whether PJ's diminished recall of a target position  
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7 462 may reflect a sensory impairment. While this seems unlikely given the finding that  
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9 463 PJ's recall precision was not significantly diminished compared to controls (with 1.0s  
10  
11 464 delay), it was important to establish the extent to which sensory difficulties may have  
12  
13 465 limited his performance. We therefore assessed participants' spatial accuracy and  
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15 466 precision in a perceptual task.  
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21 468 Experiment 3 – Methods  
22

23 469 This experiment assessed participants' ability to localise the centroid, namely the  
24  
25 470 average location, of three white discs. The discs' diameter was  $0.5^\circ$  (see figure 4A for  
26  
27 471 a schematic representation of the trial structure). The discs remained visible until  
28  
29 472 participants had positioned a crosshair shaped cursor at the desired location and  
30  
31 473 clicked the mouse. Following a blank, 1.0s-long interval, a novel set of discs appeared  
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33 474 and the procedure was repeated. Discs could occupy any of seven canonical locations.  
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35 475 These included the screen center and the vertices of a virtual concentric hexagon, with  
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37 476 a side length of  $6.87^\circ$ . All permutations of three out of seven canonical target  
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39 477 locations, less any resulting in a collinear configuration, were used as sample arrays.  
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41 478 Each possible permutation appeared twice, for a total of sixty-four trials. A  
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43 479 pseudorandom, zero mean, circular Gaussian distribution, with a standard deviation of  
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45 480  $0.6^\circ$ , was used to jitter each disc's position independently. Prior to testing,  
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47 481 instructions were read to the participants. The centroid was defined as the point in  
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49 482 space where the triangle, whose vertices coincided with the discs' locations, would  
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51 483 balance in the horizontal plane (Baud-Bovy and Soechting 2001). One of the  
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53 484 experimenters also provided a visual demonstration, using a cut-out triangular shape.  
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3 485 Prior to testing, participants completed twenty-five practice trials. At the end of each  
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5 486 practice trial, the reported and actual positions of the centroid were shown for 2.0s.  
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10 488 Experiment 3 – Data analysis

11 489 We estimated the systematic and variable error of participants' centroid estimations,  
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13 490 by fitting a linear model to the azimuth and elevation of the reported centroid  
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15 491 location. The model regressors included a constant and the centroid azimuth and  
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17 492 elevation. Two metrics were used to characterise the systematic error: 1) the constant  
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19 493 displacement, that is the tendency to report the centroid above, below, right or left of  
20  
21 494 its true location, and 2) scaling factor, measuring the linear relationship between  
22  
23 495 reported and actual centroid positions. These are, respectively, the estimated intercept  
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25 496 and beta parameters of the linear model. We computed precision as the standard  
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27 497 deviation of the variable error, i.e., residuals from the model, using the same methods  
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29 498 used in Experiment 2.  
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36 500 Experiment 3 – Results: accuracy and precision of centroid estimation

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38 501 The left-hand panels of figure 4B and 4C illustrate the direction of systematic biases  
39  
40 502 in centroid estimates. PJ and controls respectively reported the centroid  $-0.07^\circ$  and -  
41  
42 503  $0.10^\circ$  (95% CI:  $[-0.15^\circ - -0.04^\circ]$ ) left of its veridical position, suggesting that both  
43  
44 504 showed a similarly small leftward bias, ( $t(9) = 0.322$ ,  $p = 0.755$ ). However, PJ  
45  
46 505 reported the centroid  $0.56^\circ$  above its veridical position. This bias was significantly  
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48 506 larger than controls, who showed a group average upward bias of  $0.06^\circ$  (95% CI:  $[-$   
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50 507  $0.02^\circ - 0.14^\circ]$ ;  $t(9) = 3.69$ ,  $p = 0.005$ ). The middle panel of figure 4B and 4C  
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52 508 summarise the linear scaling for centroid estimates. PJ varied the reported centroid  
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54 509 azimuth by a factor of 0.97, and elevation by a factor of 1.00, in both cases reflecting  
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3 510 an almost perfect linear relationship between reported and actual centroid positions.  
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5 511 These values were comparable to those shown by controls, namely 0.99 for azimuth  
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7 512 (95% CI: [0.94 – 1.03];  $t(9) = -0.263$ ,  $p = 0.799$ ), and 0.97 for elevation (95%CI:  
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9 513 [0.93 – 1.01];  $t(9) = 0.443$ ,  $p = 0.668$ ). Finally, PJ's azimuth variable error standard  
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11 514 deviation,  $0.67^\circ$ , was not significantly different from the control average of  $0.69^\circ$   
12  
13 515 (95%CI = [ $0.56^\circ - 0.82^\circ$ ];  $t(9) = -0.091$ ,  $p = 0.931$ ), nor was his elevation variable  
14  
15 516 error standard deviation,  $0.77^\circ$ , significantly different from the control average of  
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17 517  $0.59^\circ$  (95%CI = [ $0.47^\circ - 0.70^\circ$ ];  $t(9) = 0.925$ ,  $p = 0.380$ ), suggesting that both the  
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19 518 vertical and horizontal precision of his centroid judgements was relatively spared.  
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### 25 520 Experiment 3 – Interim discussion

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27 521 PJ showed a strong tendency to report the centroid above its true location. This  
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29 522 probably represents a compensatory strategy for his upper visual field defect. In fact,  
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31 523 hemianopic patients display a bias toward their blind field when judging the midpoint  
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33 524 of horizontal line (Barton and Black 1998; Kerkhoff and Buchers 2008). However,  
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35 525 both PJs accuracy and precision estimating the centroid position were within the  
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37 526 control group's range. We conclude that aside from compensatory visual defect  
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39 527 biases, PJ's ability to localise perceptually is largely spared and unlikely to account  
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41 528 for his diminished recall precision.  
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3 530 **Discussion**

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5 531 We tested a middle-aged man (PJ) with bilateral mOTC strokes involving the PHC.  
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7 532 Acutely, PJ had developed a derangement of attention and short-term memory  
8  
9 533 (Horenstein et al. 1967; Medina et al. 1977; Shih et al. 2007). At the time of testing,  
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11 534 PJ was no longer delirious, but continued to have difficulties with his memory as well  
12  
13 535 as navigating familiar environments. The latter is a form of spatial disorientation  
14  
15 536 previously attributed to PHC lesions in humans (Zola-Morgan et al. 1989; Epstein et  
16  
17 537 al. 2001). Animal studies have demonstrated additional deficits in spatial working  
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19 538 memory following PHC lesions in non-human primates (Malkova and Mishkin 2003;  
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21 539 Bachevalier and Nemanic 2008). Whether the same deficits characterise human  
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23 540 patients with PHC lesions is not yet known.  
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29 542 We found that PJ had a profound deficit binding an object to its location in a working  
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31 543 memory task. When he recalled the colour of one of two objects, after a short memory  
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33 544 delay, he could accurately do so when the target was cued by its shape. However,  
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35 545 when the target was cued by its location, his accuracy was greatly diminished because  
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37 546 he made numerous binding errors, frequently reporting the colour of the non-target  
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39 547 item instead of the colour of the target. Control participants, on the other hand, were  
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41 548 accurate whether the target was identified by the location or shape cue. These findings  
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43 549 strongly suggest that PJ was impaired only when using a location cue and that this  
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45 550 impairment could not be attributed to either diminished memory for the report feature,  
46  
47 551 i.e. the target's colour, or a binding deficit that generalises across spatial and non-  
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49 552 spatial visual dimensions. According to a recent study, generalised binding difficulties  
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51 553 may instead characterise recall performance in individuals with autoimmune temporal  
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53 554 encephalitis, which mainly affects the hippocampal formation (Pertzov et al. 2013).  
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5 556 Some animal and imaging studies have indeed shown that both anterior PHC and  
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7 557 hippocampus contribute to object-in-place associations in short-term memory (Milner  
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9 558 et al. 1997; Bachevalier and Nemanic 2008). However, animal data suggest that  
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11 559 hippocampal involvement in spatial binding is restricted to tasks where spatial  
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13 560 relations are incidentally encoded (Bachevalier and Nemanic 2008). These findings,  
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15 561 together with ours, suggest that in tasks where spatial information is intentionally  
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17 562 encoded and recalled, the role of PHC goes beyond simply providing spatial data to  
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19 563 the hippocampus, where general purpose processes bind visual features in working  
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21 564 memory. Moreover, our findings confirm that binding in visual working memory is  
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23 565 liable to be disrupted by focal brain lesions (Gorgoraptis et al. 2011), supporting the  
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25 566 idea that it is a neural function independent from those underpinning the  
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27 567 representations of individual features (Wheeler and Treisman 2002; Smyrnis et al.  
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29 568 2005).

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36 570 Binding errors do not reflect the resolution of spatial information

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38 571 When PJ reported the location of one of three objects held in memory he erroneously  
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40 572 reported the location of one of the non-target items more frequently than controls.  
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42 573 This finding suggests that PJ had difficulties with spatial binding, whether space was  
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44 574 the cue or report dimension. One might argue that PJ's spatial binding impairment  
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46 575 simply reflects degraded spatial representations. In other words, diminished ability  
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48 576 recalling the location of an object might explain his difficulties using spatial  
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50 577 information to identify targets in memory. However, this hypothesis is not supported  
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52 578 by our data. PJ was able to estimate the centroid of simple dot configurations as  
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54 579 precisely as controls, indicating that despite the presence of an upper visual field  
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3 580 defect, the spatial resolution of visual data was not prominently affected in this  
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5 581 perceptual task. Moreover, PJ's precision recalling the location of visual targets was  
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7 582 not appreciably different from that of controls, even though his proportion of spatial  
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9 583 binding errors was much greater. Finally, binding errors did not become more  
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11 584 frequent when the delay interval was increased, although the precision of spatial recall  
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13 585 did decrease. We conclude that binding errors do not reflect the temporal decay of a  
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15 586 memory trace, contrary to previous suggestions (Zhang and Luck 2009). Moreover,  
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17 587 our findings are consistent with observations that binding errors are not affected by  
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19 588 the duration of the memory delay in either patients with hippocampal pathology  
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21 589 (Pertzov et al. 2013) or healthy controls (Gorgoraptis et al. 2011), although whether  
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23 590 binding errors may be effected by longer (e.g., >20.0s) delays remains to be  
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25 591 established. Finally, varying the spatial memory demands at the time of recall in a  
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27 592 spatial version of the Sternberg working memory task does not change the likelihood  
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29 593 of committing a binding error, confirming that binding errors do not reflect confusion  
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31 594 among features of the probe dimension (Smyrnis et al. 2005). Taken together, the  
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33 595 available evidence in healthy controls and patients instead suggests that binding errors  
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35 596 reflect interference with early processes, engaged at the time when visual information  
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37 597 is encoded in working memory. **However, a recent high-resolution fMRI study has**  
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39 598 **suggested that load dependent signals in PHC during the delay period of a match-to-**  
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41 599 **sample-task may reflect on-going binding processes (Schon et al. 2016).**  
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#### 601 Delays affect the precision of spatial recall

602 PJ's spatial recall precision was similar to that of controls when the memory delay  
603 lasted 1.0s. When the memory delay was 5.0s long, both he and controls suffered a  
604 decrement in recall precision. These are not entirely novel findings. Recall precision

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3 605 is known to decrease with longer memory delays in healthy controls (Sheth and  
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5 606 Shimojo 2001; Zhang and Luck 2009). Moreover, recall precision disproportionately  
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7 607 decreases in patients with PHC lesions, although significantly so only following  
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9 608 memory delays greater than 20s (Ploner et al. 2000). This finding is in keeping with  
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11 609 our own: recall efficiency following 5.0s vs 1.0s delays was lower in PJ than in  
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13 610 controls, however this difference was not significant. Combined, these data are  
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15 611 consistent with the idea that following PHC lesions, spatial recall precision decays  
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17 612 more quickly than in healthy controls, as opposed to declining abruptly. More  
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19 613 generally, our findings are in keeping with the view that spatial recall draws  
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21 614 information from a limited capacity resource (Bays et al. 2009), whose resolution  
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23 615 diminishes over time. Therefore, delay dependent changes in spatial recall precision  
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25 616 most likely reflect a limited ability to maintain information in working memory rather  
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27 617 than impaired encoding, in contrast to the binding deficits discussed above. Finally,  
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29 618 PJ's performance in our experiments is consistent with his neuropsychological profile,  
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31 619 which is principally characterised by impairment on various memory tasks, including  
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33 620 those that do not have a spatial binding component, such as the Logical Memory test  
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35 621 and the Rey Auditory Verbal Learning Test. However we do not yet know the extent  
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37 622 to which diminished recall precision and spatial binding account for the broad  
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39 623 memory deficits observed following lesions to PHC.  
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47 Could the hippocampus be the site for short term memory spatial binding?

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49 626 In the present study we identified impairments resulting from focal lesions to PHC,  
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51 627 and found a spatial binding deficit in short term memory. Our data cannot rule out the  
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53 628 possibility that binding takes place outside PHC, for example, in the hippocampus.  
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56 629 Indeed, comparison of hippocampal volumes in PJ and age and gender matched  
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3 630 controls suggest hippocampal atrophy in PJ. Lateralised hippocampal atrophy  
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5 631 commonly follows distal, ipsilateral stroke, even in young patients unlikely to harbour  
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7 632 neurodegenerative processes (Schaapsmeeders et al. 2015a, 2015b), suggesting that  
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9 633 the hippocampus may be particularly vulnerable to the effects of deafferentation. Pj's  
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11 634 hippocampal atrophy raises the possibility that spatial binding deficits reflect  
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13 635 diminished function within the hippocampus. Our data cannot refute this alternative  
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15 636 hypothesis. As mentioned in the introduction, previous studies in patients with  
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17 637 inflammatory and anoxic damage involving the hippocampus (e.g. Pertzov et al.  
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19 638 2013; Watson et al. 2013; Yee et al. 2014) have also demonstrated spatial binding  
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21 639 impairments, lending support to the hippocampus' role in feature binding.  
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23 640 Nonetheless, the specific spatial nature of PJ's binding impairment, which did not  
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25 641 generalise to other visual dimensions (i.e., shape), is inconsistent with the proposal  
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27 642 that the hippocampus provides a general purpose binding mechanism. Therefore, we  
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29 643 conclude that spatial binding is either carried out in hippocampus, using inputs from  
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31 644 PHC, or that PHC itself initiates spatial binding processes.  
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#### 646 Concluding remarks

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41 647 This study provides novel information on the role of MTL, by showing that a man  
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43 648 with a lesion involving PHC, hippocampal atrophy, but spared PRC, has a selective  
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45 649 deficit in short term spatial binding. This deficit is not explained by diminished  
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47 650 resolution of spatial information. Our findings are consistent with the idea that spatial  
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49 651 binding processes in short term memory may be initiated in the PHC even before  
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51 652 visual information reaches the hippocampus.  
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For Peer Review

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**Tables**

Neurocognitive domain / Test / Subtest	Raw score	Standard/Z Score	Percentile
<b>Intellectual Functioning</b>			
<i>Wechsler Intelligence Scale - IV</i>			
Full Scale IQ		87	19
Verbal Comprehension Index		96	39
Perceptual Reasoning Index		90	25
Working Memory Index		92	25
Processing Speed Index		79	8
Vocabulary		9	37
Similarities		9	37
Information		10	50
Block Design		9	37
Matrix Reasoning		5	5
Visual Puzzles		11	63
Digit Span		9	37
Arithmetic		8	25
Symbol Search		7	16
Coding		5	5
<b>Learning and Memory</b>			
<i>Wechsler Memory Scale</i>			
Logical Memory I	11/75	2	0.4
Logical Memory II	4/50	3	1
Visual Reproduction I	56	4	2

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3	Visual Reproduction II	13	5	5
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5	<i>Auditory Verbal Learning Test</i>			
6				
7	Trial I	3	-2	2
8				
9	Trial II	4	-2.33	1
10				
11	Trial III	5	-2	2
12				
13	Trial IV	8	-1.15	13
14				
15	Trial V	5	-3.31	1
16				
17	List B	4	-1.11	13
18				
19	Trial VI	3	-2.2	2
20				
21	Delayed Recall	1	-2.54	1
22				
23	Recognition	1	-4.3	1
24				
25				
26				
27	<i>Rey Complex Figure Test</i>			
28				
29	Copy	36	1.38	92
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31	30 minute recall	1.5	-2.25	< 1
32				
33				
34	<i>Benton Visual Retention Test</i>			
35				
36	Correct score	3	-2.69	< 1
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38	Error score	13	-3.35	< 1
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42	<b>Attention/Executive Function</b>			
43				
44	<i>Trail Making Test</i>			
45				
46	Part A	72 sec	-4.05	< 1
47				
48		131		
49	Part B		-4.66	< 1
50		sec		
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53	<i>D-K Executive Function System</i>			
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55	Verbal Fluency Test			
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Letter Fluency	25	6	9
Category Fluency	39	10	50
<i>Tower Test</i>			
Total Achievement Score	16	10	50
<i>Stroop Test</i>			
Colour task	112		
Colour-word task	38		> 2

## Object recognition and Space

### Perception

#### *The Visual Object and Space Perception*

##### *Battery*

##### *Object Perception*

Screening Test	20/20 (Pass)
Incomplete Letters	19/20 (Pass)
Silhouettes	19/30 (Pass)
Object Decision	17/20 (Pass)
Progressive Silhouettes	11 (Fail)

##### *Space Perception*

Dot Counting	10/10 (Pass)
Position Discrimination	20/20 (Pass)
Number Location	10/10 (Pass)
Cube Analysis	10/10 (Pass)

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911 *Table 1. Summary of PJ's neuropsychometric performance six months after stroke.*

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Gender	Handed	Age	IQ	Age Leaving School
M	Right	51	106	18
M	Right	43	111	16
M	Right	45	99	16
M	Right	61	103	17
M	Right	39	109	18
M	Right	47	90	16
M	Right	53	88	16
M	Right	46	104	17
M	Right	53	97	16
M	Right	44	104	16
	<b>Mean</b>	48.2	101.1	16.6
	<b>SD</b>	6.4	7.6	0.8

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*Table 2. Control group demographics and IQ*

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3 926 **Captions**

4  
5 927 Figure 1. Lesion anatomy. T1 weighted, MNI atlas registered axial (panel A) and  
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7 928 coronal (panel B) slices are displayed in neurological coordinates, and illustrate the  
8  
9 929 extent of ischemic damage in the left and right mOTC. In panel A, the axial slices  
10  
11 930 also highlight the location of entorhinal and perirhinal cortex, in red and green  
12  
13 931 respectively. These regions lay anteriorly and laterally to the boundaries of the  
14  
15 932 ischemic lesions. In panel B, coronal slices highlight parahippocampal and  
16  
17 933 hippocampal structures, including the fornix. The ischemic lesions lay inferiorly and  
18  
19 934 posteriorly to the hippocampus and spare the fornix and the retrosplenial cingulate  
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21 935 cortex.  
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26 936  
27 937 Figure 2. Spatial vs. non-spatial binding in working memory. Panel A shows the trial  
28  
29 938 structure. The sample display for all participants (including PJ) contained a square  
30  
31 939 and a triangle, placed side by side in the bottom half of the screen. The two objects  
32  
33 940 were red, blue or green and never had the same colour. After a brief pattern mask and  
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35 941 blank delay, three vertical coloured bars appeared as well as a cursor, which the  
36  
37 942 participant used to report the colour of the memory target. In shape trials, targets were  
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39 943 identified by a probe whose outline matched the target shape. In location trials, the  
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41 944 location of targets were identified by a white cross. Panel B shows each individual  
42  
43 945 participants' error rate on a greyscale, with lighter colours representing a higher  
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45 946 proportion of errors; the left panel shows generic errors, the right panel shows binding  
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47 947 errors. On each panel, the upper row shows errors following shape probes, while the  
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49 948 lower row shows errors following location probes, for PJ (blue outline) and each of  
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51 949 the controls (red outline). Panel C shows PJ's and the group averaged proportion of  
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53 950 generic and binding errors. Error bars are standard error of the mean.  
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5 952 Figure 3. Delayed spatial recall. Panel A shows the structure of immediate and  
6  
7 953 delayed, spatial recall trials. The sample display for all participants (including PJ)  
8  
9 954 contained three coloured discs, which could appear in both the upper and lower  
10  
11 955 portion of the screen. The participants had to reproduce the position of one of the  
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14 956 discs (the target) using a mouse cursor after either a 1.0s pattern mask or an additional  
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16 957 4.0s delay. The target was identified by its colour, indicated by a visual probe  
17  
18 958 displayed at the center of the screen. Panel B (left) shows PJ's (blue outline) and  
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20 959 controls' (red outline) individual percentage of binding errors on a greyscale,  
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22 960 following 1.0s (upper row) and 5.0s (lower row) delays, with lighter colours  
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24 961 representing a higher proportion of errors. Panel B (right) shows recall precision (95%  
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26 962 error ellipses) in 1.0s and 5.0s delayed recall trials for PJ (blue) and controls (red).  
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28 963 Panel C shows PJ's and the group averaged proportion of binding errors and  
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30 964 precision. Error bars are standard error of the mean.  
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36 966 Figure 4. Centroid estimation. Panel A shows the trial structure. The participants  
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38 967 placed a cursor at the centroid of the configuration formed by three bright discs. The  
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40 968 discs remained visible until the participant made a response by clicking the mouse.  
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43 969 Panel B shows each participant's constant displacement (arrow vectors), scaling  
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45 970 (diamond plot) and precision (uncertainty ellipses) in locating the centroid. The length  
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47 971 of the diamond plot's hemi-axes corresponds to 1.0 scaling factor. Panel C shows PJ's  
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49 972 and group averaged values of the constant displacement and scaling factor, separately  
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51 973 for azimuth (X) and elevation (Y). The precision measure shown is the square root of  
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53 974 the mean error variance for azimuth and elevation. Error bars in all cases are standard  
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55 975 error of the mean.  
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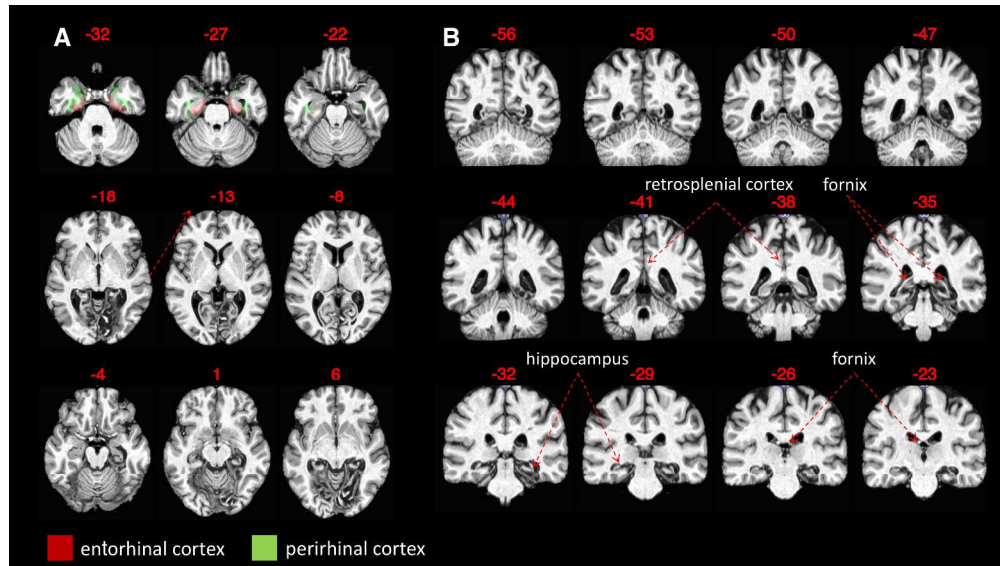


Figure 1. Lesion anatomy. T1 weighted, MNI atlas registered axial (panel A) and coronal (panel B) slices are displayed in neurological coordinates, and illustrate the extent of ischemic damage in the left and right mOTC. In panel A, the axial slices also highlight the location of entorhinal and perirhinal cortex, in red and green respectively. These regions lay anteriorly and laterally to the boundaries of the ischemic lesions. In panel B, coronal slices highlight parahippocampal and hippocampal structures, including the fornix. The ischemic lesions lay inferiorly and posteriorly to the hippocampus and spare the fornix and the retrosplenial cingulate cortex.

1375x773mm (72 x 72 DPI)

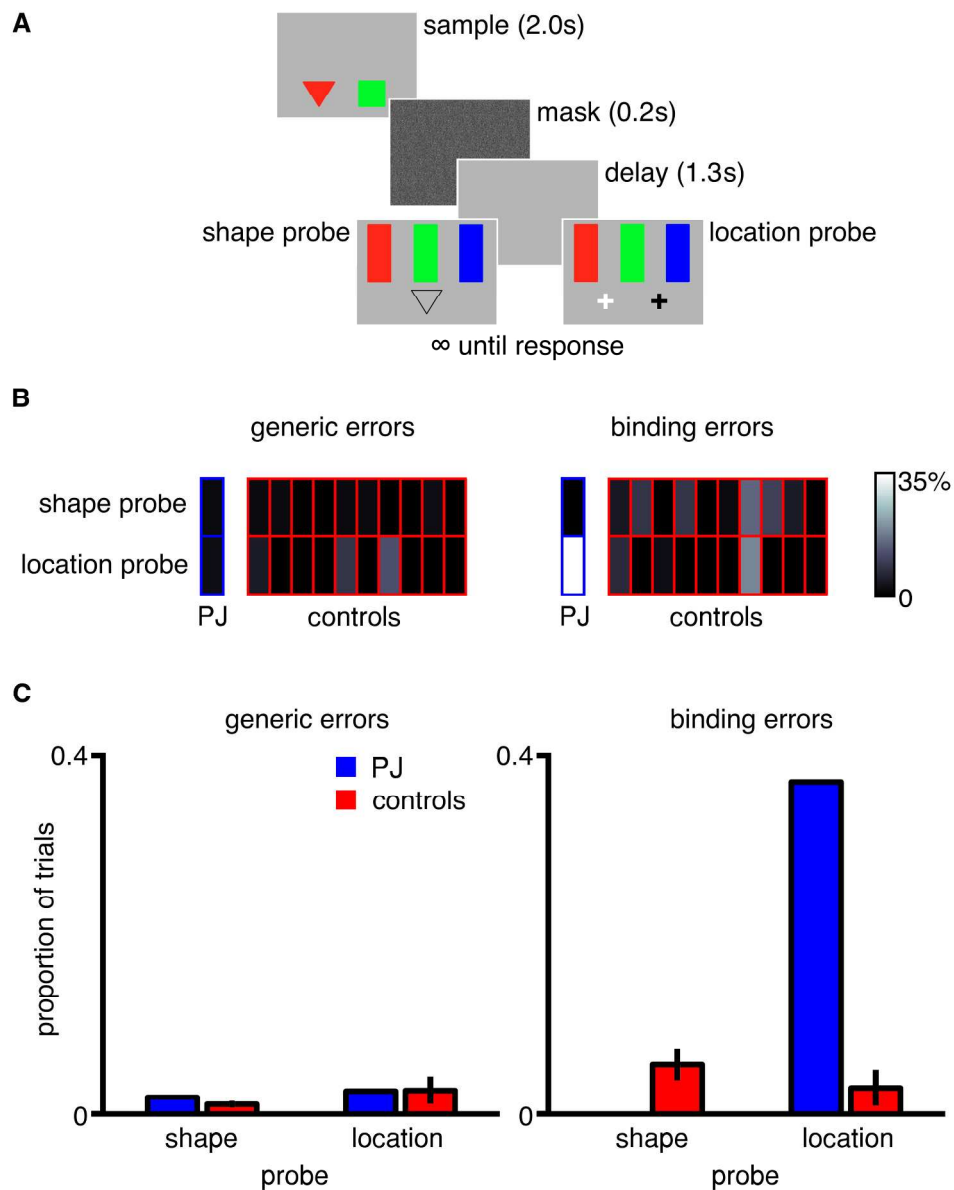


Figure 2. Spatial vs. non-spatial binding in working memory. Panel A shows the trial structure. The sample display for all participants (including PJ) contained a square and a triangle, placed side by side in the bottom half of the screen. The two objects were red, blue or green and never had the same colour. After a brief pattern mask and blank delay, three vertical coloured bars appeared as well as a cursor, which the participant used to report the colour of the memory target. In shape trials, targets were identified by a probe whose outline matched the target shape. In location trials, the location of targets were identified by a white cross. Panel B shows each individual participants' error rate on a greyscale, with lighter colours representing a higher proportion of errors; the left panel shows generic errors, the right panel shows binding errors. On each panel, the upper row shows errors following shape probes, while the lower row shows errors following location probes, for PJ (blue outline) and each of the controls (red outline). Panel C shows PJ's and the group averaged proportion of generic and binding errors. Error bars are standard error of the mean.

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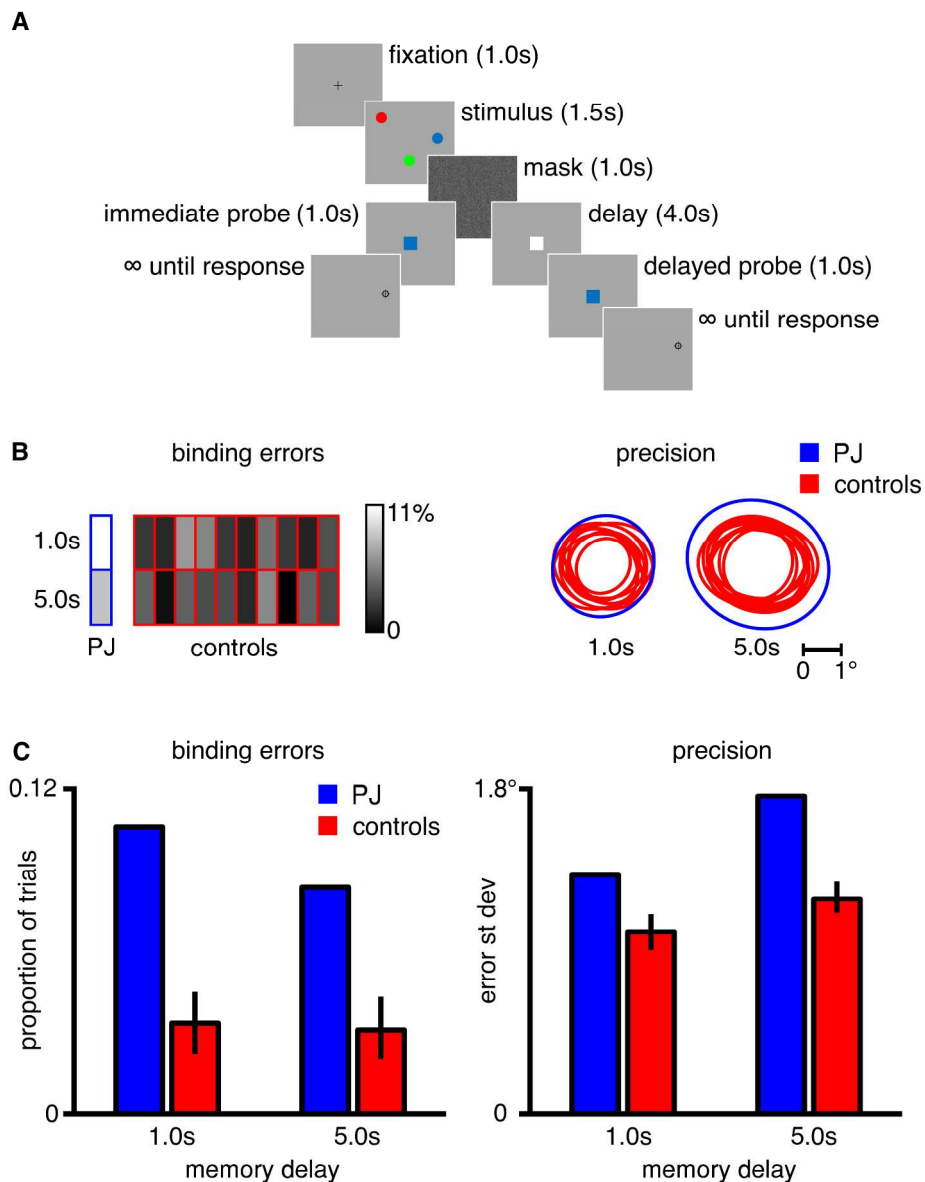


Figure 3. Delayed spatial recall. Panel A shows the structure of immediate and delayed, spatial recall trials. The sample display for all participants (including PJ) contained three coloured discs, which could appear in both the upper and lower portion of the screen. The participants had to reproduce the position of one of the discs (the target) using a mouse cursor after either a 1.0s pattern mask or an additional 4.0s delay. The target was identified by its colour, indicated by a visual probe displayed at the center of the screen. Panel B (left) shows PJ's (blue outline) and controls' (red outline) individual percentage of binding errors on a greyscale, following 1.0s (upper row) and 5.0s (lower row) delays, with lighter colours representing a higher proportion of errors. Panel B (right) shows recall precision (95% error ellipses) in 1.0s and 5.0s delayed recall trials for PJ (blue) and controls (red). Panel C shows PJ's and the group averaged proportion of binding errors and precision. Error bars are standard error of the mean.

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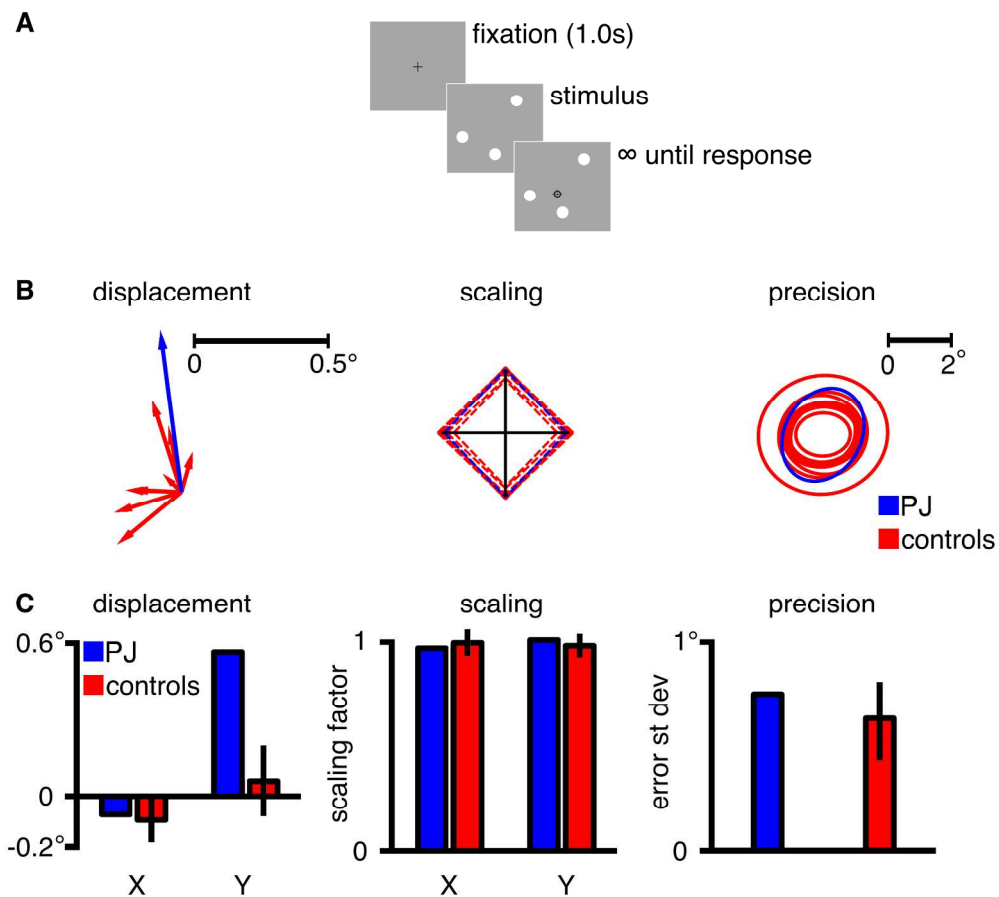


Figure 4. Centroid estimation. Panel A shows the trial structure. The participants placed a cursor at the centroid of the configuration formed by three bright discs. The discs remained visible until the participant made a response by clicking the mouse. Panel B shows each participant's constant displacement (arrow vectors), scaling (diamond plot) and precision (uncertainty ellipses) in locating the centroid. The length of the diamond plot's hemi-axes corresponds to 1.0 scaling factor. Panel C shows PJ's and group averaged values of the constant displacement and scaling factor, separately for azimuth (X) and elevation (Y). The precision measure shown is the square root of the mean error variance for azimuth and elevation. Error bars in all cases are standard error of the mean.

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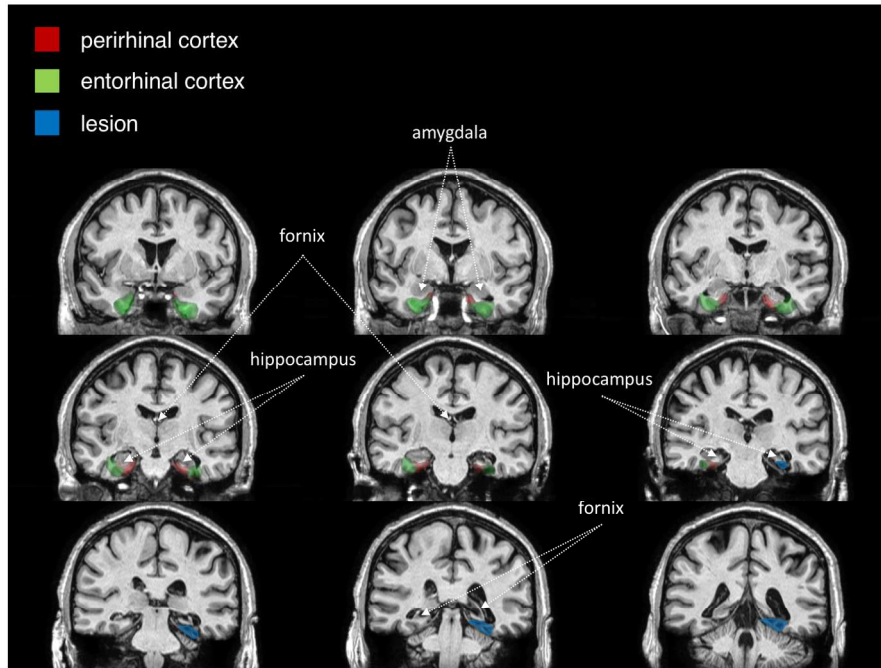


Figure S1. Multiple, MNI atlas registered coronal slices are displayed in neurological coordinates and show the relation between entorhinal and perirhinal cortex, and ischemic tissue, allowing a clearer depiction of the anatomical relation between these structures. The figure indicates that entorhinal and perirhinal cortex were spared by the ischemic event.

791x594mm (72 x 72 DPI)

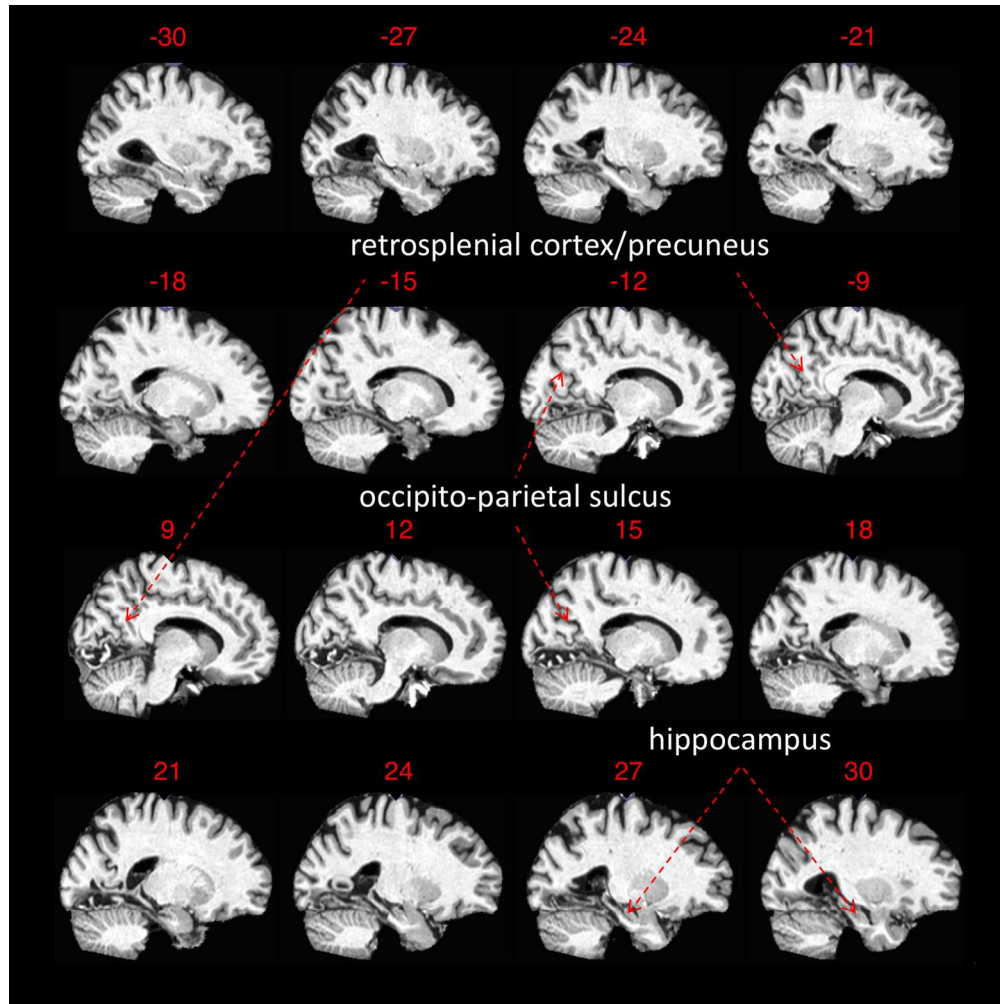


Figure S2. Multiple MNI atlas registered sagittal slices depict the relation between hippocampus and the lesioned parahippocampal and lingual cortex, in both hemispheres. Also, the retrosplenial cingulate cortex and the precuneus are fully visible and show no evidence of ischemic damage.

791x793mm (72 x 72 DPI)

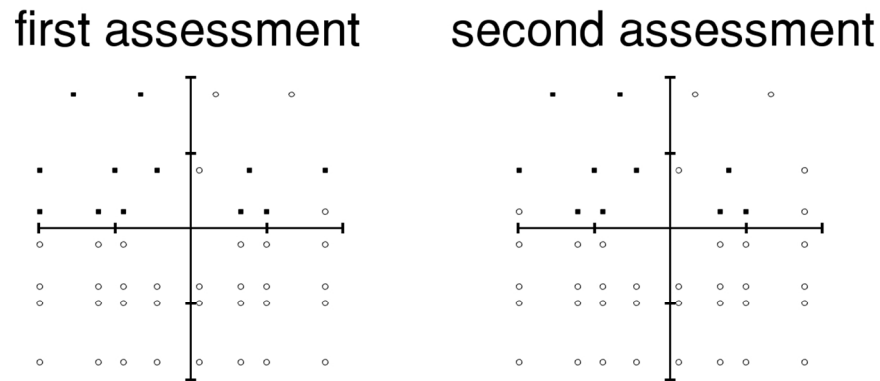


Figure S3. PJ's visual perimetry assessed three months (left panel) and five months (right panel) following the ischemic injury. Perimetry was measured with a binocular field test (Esterman, 1982). Hash marks on both the x and y axis indicate increments of ten visual degrees. Empty squares indicate hits, while filled squares indicate locations where PJ failed to report a target. PJ showed strict upper quadrantanopias, worse on the left than on the right. On the second assessment, PJ detected targets in the left and right upper visual field, at locations  $(-10.0^{\circ}, 2.29^{\circ})$  and  $(17.6^{\circ}, 7.90^{\circ})$ , that he previously missed, suggesting partial recovery.

493x205mm (72 x 72 DPI)

Peer Review

### Supplementary figure captions

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6 Figure S1. Multiple, MNI atlas registered coronal slices are displayed in neurological  
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20 Figure S2. Multiple MNI atlas registered sagittal slices depict the relation between  
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33 Figure S3. PJ's visual perimetry assessed three months (left panel) and five months (right  
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