No effect of hippocampal lesions on stimulus-response bindings

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ABSTRACT

The hippocampus is believed to be important for rapid learning of arbitrary stimulus-response contingencies, or S-R bindings. In support of this, Schnyer et al. (2006) (Experiment 2) measured priming of reaction times (RTs) to categorise visual objects, and found that patients with medial temporal lobe damage, unlike healthy controls, failed to show evidence of reduced priming when response contingencies were reversed between initial and repeated categorisation of objects (a signature of S-R bindings). We ran a similar though extended object classification task on 6 patients who appear to have selective hippocampal lesions, together with 24 age-matched controls. Unlike Schnyer et al. (2006), we found that reversing response contingencies abolished priming in both controls and patients. Bayes Factors provided no reason to believe that response reversal had less effect on patients than controls. We therefore conclude that it is unlikely that the hippocampus is needed for S-R bindings.

1. Introduction

The medial temporal lobes (MTL), and hippocampus in particular, are thought necessary for rapid acquisition of new associations (Squire, 1992; Cohen and Eichenbaum, 1994; Schacter and Tulving, 1994; Giovanello et al., 2004). On the other hand, such MTL regions do not appear necessary for all types of rapid plasticity, such as that presumed to underlie phenomena like priming, which can also occur after a single exposure to a stimulus (e.g., Cave and Squire, 1992; Schacter et al., 1993). Priming is often measured by decreases in the reaction time (RT) to perform a simple classification task on a stimulus, such as deciding whether the object depicted by a picture is large or small in real life. Such RT priming has often been associated with facilitated perceptual or conceptual processing, occurring in cortical regions outside the MTL (Moscovitch, 1994).

However, recent studies have shown that the dominant cause of such classification-based RT priming is the encoding and retrieval of Stimulus-Response (S-R) bindings (see Henson et al., 2014, for a recent review). According to this account, the response made to the first presentation of a stimulus is bound together with that stimulus, such that when that stimulus is repeated, the response can be retrieved. This retrieval of a previous response is assumed to be faster than repeating the original perceptual/conceptual processing that generated the

response on the initial stimulus presentation, causing the RT priming. However, if the task changes between initial and repeated presentations, such that the response is changed, the amount of RT priming is reduced. Indeed, sometimes priming is abolished by a response reversal, or even becomes negative, i.e, slower RTs for repeated than novel stimuli, possibly owing to interference from retrieval of incorrect responses (Horner and Henson, 2011). This difference in the amount of priming as a function of whether or not the response on second presentation is congruent with that on first presentation – the "congruency effect" – is often used as the defining signature of S-R bindings.

Neuroimaging data support the contribution of rapidly learnt S-R bindings to performance on classification tasks. Several fMRI studies in healthy individuals have found that the decreased fMRI response following repetition of visual stimuli ("repetition suppression", RS), which has been associated with priming (Koutstaal et al., 2001; Schacter and Buckner, 1998; Simons et al., 2003), is reduced when the classification task is reversed. This reduction in RS following response reversal has been seen in lateral prefrontal regions commonly associated with response selection, and occasionally in ventral temporal regions commonly associated with perceptual/conceptual component processes (Dobbins et al., 2004; Horner and Henson, 2008; Race et al., 2009), though is not readily apparent in MTL regions.

Given that a typical priming experiment entails tens if not hundreds

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of unique stimuli, the retrieval of the appropriate S-R binding when one of those stimuli is repeated suggests that the brain has an impressive capacity to store many such S-R bindings. To test whether this capacity for rapid learning of multiple, unique S-R associations is supported by MTL, Schnyer et al. (2006; Experiment 2) reported priming data from a speeded classification task on nine patients with MTL damage, together with age-matched controls. Participants were initially asked to decide "Is the object bigger than a shoebox?", but then after one or three presentations of each stimulus, the task reversed to "Is the object smaller than a shoebox?". Controls showed the usual reduction in RT priming when the task was reversed, indicative of S-R bindings. RT priming in the patients however showed no detectable effect of the task being reversed (see ahead to Fig. 3 for a re-plotting of Schnyer et al.'s data). The authors therefore concluded that MTL regions are responsible for S-R learning.

Though MTL damage was "radiologically-verified" in each patient, the extent of that damage was not reported by Schnyer et al. (2006), so they were unable to conclude whether S-R bindings are supported specifically by the hippocampus, or by other MTL regions like entorhinal, perirhinal or parahippocampal cortices. We recently reported six patients whose MRI scans showed clear evidence of hippocampal volume reduction, with little sign of gray-matter damage outside the hippocampus (Henson et al., 2016). Our main aim in the present experiment was therefore to determine whether the S-R deficit reported by Schnyer et al. is specific to hippocampal damage.

Our second aim was to test whether Schnyer et al.'s results generalise to a modified version of the object classification task. Our modified paradigm (initially proposed by Denkinger and Koutstaal (2009) involves keeping the task constant (e.g, "Is the object bigger than X?"), but changing the referent instead (i.e, X). This paradigm simultaneously reverses all three levels of response representations in S-R bindings that have been identified to date (Horner and Henson, 2011; see also Schnyer et al., 2007; Dennis and Perfect, 2012). This is illustrated in Fig. 1, where the response associated with an object (e.g, monkey) when it is judged to be bigger than a shoebox could include the specific motor Action (e.g, right index finger press), the Decision (e.g, "yes"/"no") and/or the Classification label (e.g, "bigger"/ "smaller"). Reversing the task, as done in the Schnyer et al. paradigm, potentially disrupts the value of retrieving the previous Action and/or Decision (i.e, disrupts S-A and/or S-D bindings), but retrieving the previous Classification label (e.g., "bigger") could still help generate a response (e.g, "no" to the reversed task of "smaller than a shoebox?"). Note that we use to term "classification" to refer to the binary category label given to the object at Study (e.g., "bigger" or "smaller"); more complex stimulus-task associations, or semantic information about the objects, are also likely to contribute to priming in general, but are kept constant in the current paradigm (see Discussion section for fuller consideration of these issues). Indeed, it is possible that the residual priming in Schnyer et al.'s reversal condition, which they attributed to facilitation of perceptual/conceptual processes outside the MTL, actually reflected intact stimulus-classification (S-C) bindings in their patients (despite impaired S-A and/or S-D bindings). On the other hand, changing the referent, for example to a wheelie bin[1] (Fig. 1), additionally disrupts the value of retrieving a prior Classification, as shown by Horner and Henson (2009), and may therefore abolish any priming in patients with hippocampal damage.

Furthermore, we can also test the type of stimulus representation in S-R bindings by orthogonally varying whether or not the stimulus is repeated in the same perceptual form (e.g, picture or word) as its initial presentation. We previously showed evidence for two levels of stimulus representation: a form-specific and more abstract representation

(Horner and Henson, 2011; see also Allenmark et al., 2015; though see Schnyer et al., 2007). We included this "Within-format" versus "Across-format" manipulation in the present experiment to test whether patients are similarly able to form S-R bindings that abstract away from the precise stimulus form. Indeed, the present experiment is identical to that in Experiment 1 of Horner and Henson (2011), except that we: 1) tested older healthy controls and patients, rather than young controls, 2) made trials self-paced rather than running at a fixed rate, to make the task easier for patients (and older controls), who generally respond slower and show greater variability, and 3) used two rather than three presentations of each stimulus before the referent change, to try to maintain the same total duration as our previous experiment.

More precisely, Experiment 1 conformed to a $2 \times 3 \times 2$ factorial design, with between-subject factor Group (N = 24 Controls vs N = 6 Patients) and within-subject factors: Study Condition (Within-format Primed, Across-format Primed, Novel) and Congruency (Congruent, Incongruent; see Methods section for how Novel trials were split into Congruent and Incongruent conditions). Like Horner and Henson (2011), we defined priming in multiple ways, but focus on the proportional measure ((Novel–Primed)/Novel) used by Schnyer et al. (2006) to allow for the fact that patients tend to have longer overall RTs than controls. Once priming scores have been calculated, the design equates to a 2 (Group) $\times$ 2 (Format) $\times$ 2 (Congruency) factorial design. Based on Schnyer et al.'s findings, we expected an interaction between Group and Congruency on the amount of priming, with controls showing a greater effect of congruency than patients. More specifically, we predicted that controls would show greater priming than patients in Congruent trials (because controls but not patients benefit from S-R bindings), but comparable or even less priming than patients for Incongruent trials (where controls would either ignore S-R bindings, or experience interference from incompatible S-R bindings).

2. Materials and methods

2.1. Participants

The six patients were selected from the Cambridge Hippocampal Panel, and are the same as those reported in Henson et al. (2016). The study was approved by NRES Ethics Committee East of England (ref 12/ EE/0190) and written consent obtained according to the Declaration of Helsinki. The patients were referred on the basis of reported memory difficulties and, in some cases, a diagnostic MR scan that showed an indication of limited MTL damage.

A summary of the patients is given in Table 1. The Z-scores for verbal memory, visuospatial memory, verbal memory, visuospatial skills and executive function are combined across multiple neuropsychological tests (using Stouffer's method; see Henson et al., 2016, for details and scores of precise tests). All patients were impaired in verbal and/or visual memory: although the combined Z-score was not significant for P5, this was driven by intact recognition memory (75–95th percentile for words; 50th percentile for faces), and when restricted to recall tests, her memory varied from 10 to 25th percentile for stories and 2–25th percentile for complex figures (see Henson et al., 2016). The only non-memory impairment was executive function for P4 (see Supplementary Material for analyses with P4 excluded). All six patients showed significant reduction in hippocampal volume; two showed additional reduction in entorhinal volume (P4 and P6) and two showed additional reduction in parahippocampal volume (P2 and P6). Whole-brain voxel-wise analysis did not reveal any significant group differences from age- and sex-matched controls outside the hippocampus (Henson et al., 2016).

Twenty-four control participants were recruited from the Volunteer Panel of the Medical Research Council (MRC) Cognition and Brain Sciences Unit (CBU). There was no significant difference in the ages of these controls (M = 60, range 50–72) and those of the patients (M = 58, range 39–66), in terms of the mean, t(28) = 0.54, p = 0.60, or the

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[1] Wheelie bin is a common term in the United Kingdom that refers to a large trash can (with wheels), which has a standard size (approx 1 m × 0.6 m × 0.7 m; 240 l) that would be well-known by our participants.