

RAPID COMMUNICATION

Successful Transverse Patterning in Amnesia Using Semantic Knowledge

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ABSTRACT: We examined whether alternate systems compensate for deficient ones to process relations in amnesia. Transverse patterning (TP), a test of relating items to one another in memory, is reliably impaired in amnesia and has played a central role in testing hippocampal function. We facilitated successful TP in amnesia by providing familiar stimuli with semantically meaningful relationships. Tapping semantic knowledge allowed TP to be solved via extrahippocampal structures. Our work shows that by framing a situation as meaningful we can engage alternate neural systems to compensate for impairments. © 2007 Wiley-Liss, Inc.

KEY WORDS: hippocampus; memory; transverse patterning; learning; amnesia

INTRODUCTION

Amnesia typically results from bilateral damage to the hippocampus (Scoville and Milner, 1957; Victor and Agamanolis, 1990). Although some memory functions remain intact following hippocampal damage, the ability to learn and remember relationships among multiple items is impaired (Cohen and Eichenbaum, 1993; Rudy and O'Reilly, 2001; Moses and Ryan, 2006).

A quintessential example of a task involving memory for relationships among multiple items is transverse patterning (TP). TP is structurally analogous to the childhood game “rock-paper-scissors” (RPS), but uses novel stimuli (A, B, C) that have ambiguous meanings outside the context of their combinations (A+ B–, B+ C–, C+ A–). TP cannot be solved without knowledge of the relationships among the stimuli. Learning about the prior reinforcement history of the individual elements (i.e., associative learning) is insufficient because each item is rewarded and unrewarded an equal number of times, and is hence considered a configural/nonlinear problem (Sutherland and Rudy, 1989; Driscoll et al., 2005).

Nonlinear problems, such as TP, are proposed to rely on the hippocampus, whereas elemental problems that can be acquired via associative learning are thought to be hippocampal independent (Sutherland and

Rudy, 1989; Rudy and Sutherland, 1995; Driscoll et al., 2005). Damage to the hippocampus leads to retrograde amnesia for previously learned TP and elemental problems (Driscoll et al., 2005). However, successful postmorbidity acquisition of the elemental problems is observed in rats and humans, with impaired acquisition of TP (Alvarado and Rudy, 1995; Driscoll et al., 1995; Rickard and Grafman, 1998). Therefore, TP is reliably impaired in amnesia and plays a central role in testing hippocampal function (Alvarado and Rudy, 1995; Rickard and Grafman, 1998; Driscoll et al., 2003; Driscoll et al., 2005; Rickard et al., 2006).

We questioned whether we could manipulate stimulus parameters to observe intact processing of relations in the TP task following hippocampal damage. Recent evidence suggests that other tasks thought to depend on the hippocampus, such as allocentric spatial navigation in a premorbidly familiar environment, can be maintained following hippocampal lesions in humans (Corkin, 2002; Rosenbaum et al., 2000). This phenomenon can be replicated experimentally in rats by providing extensive premorbid experience with a given set of contextual cues from multiple perspectives, for example by rearing rats in the testing environment (Winocur et al., 2005). Therefore, although allocentric spatial navigation is often mediated by the hippocampus, this task can be maintained following hippocampal lesions, providing that the cues are extensively experienced premorbidly from a variety of different perspectives. This process is thought to be analogous to the creation of semantic memories, which remain intact and accessible following hippocampal lesions (Rosenbaum et al., 2001).

In a similar vein, we asked whether the nonlinear TP task could be mediated by extra-hippocampal structures if the stimuli or relationships involved were premorbidly familiar. In the current study we attempted to facilitate intact TP in an amnesic individual with extensive bilateral hippocampal damage by using semantically meaningful stimuli to tap knowledge mediated by alternate systems and promote processing of relationships via extra-hippocampal struc-

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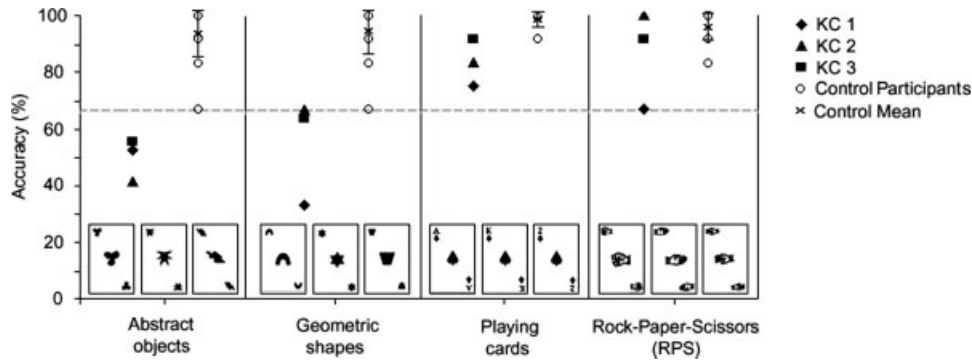


FIGURE 1. Transverse patterning test blocks. Error bars denote 99% confidence interval (CI). Dotted line denotes 67% theoretical maximum indicative of an elemental strategy. Abstract objects: K.C.'s accuracy was 53% in Session 1, 42% in Session 2 and 56% in Session 3. Performance was below the control range (mean = 94% (CI = 85–100%), and well below the elemental theoretical maximum. Geometric shapes: K.C.'s accuracy was 33% in Session 1, 67% in Session 2, and 64% in Session 3. Performance was below the control range (mean = 95%; CI = 86–100%),

and did not exceed the elemental theoretical maximum. Playing cards: K.C.'s accuracy was 75% in Session 1, 83% in Session 2 and 92% in Session 3. Performance overlapped the control range, nearing the CI, in Session 3 (mean = 99%; CI = 96–100%), and was well above the elemental theoretical maximum for Sessions 2 and 3. Rock-paper-scissors (RPS): K.C.'s accuracy was 67% in Session 1, 100% in Session 2 and 92% in Session 3. Performance in Sessions 2 and 3 overlapped the control CI (mean = 96%; CI = 91–100%).

tures. We employed four conditions that varied on whether the stimuli and relationships among them were known preexperimentally and, therefore, had varying degrees of semantic meaningfulness: (1) RPS; (2) playing cards; (3) familiar geometric shapes; (4) abstract objects (Fig. 1). Thus, Conditions 1–3 used familiar stimuli, but only the stimuli in Conditions 1 and 2 had familiar relationships. We hypothesized that the use of previously acquired semantic relationships could support performance via extra-hippocampal structures.

We tested the amnesic case K.C., age 55, who sustained multifocal and diffuse brain damage, including almost complete bilateral hippocampal loss. K.C. is a right-handed man with 16 yr of education who became profoundly amnesic following a closed-head injury in 1981. Extensive neuropsychological assessment confirmed extensive and severe retrograde and anterograde amnesia, but otherwise intact intellectual, visuospatial, language, and executive functions. K.C. retains premorbidly acquired semantic memories (Rosenbaum et al., 2005). Recent magnetic resonance imaging (MRI) indicates volume loss in the medial temporal lobes that is most pronounced in the hippocampal formation and neighboring parahippocampal gyrus bilaterally. Lateral temporal cortex appears to have been spared from focal damage. Also relevant to the present study is the finding of a large lesion in left occipital-temporal-parietal cortex, affecting mostly lingual gyrus and cuneus up to medial retrosplenial cortex, and a lesion in left frontal-parietal cortex, undercutting postcentral gyrus and extending across superior precentral and premotor cortex into dorsolateral prefrontal cortex. Signal abnormalities in the right hemisphere are generally limited to the precuneus. For an in-depth description of neuropsychological and neuroanatomical findings, see Rosenbaum et al. (2005).

K.C. completed all TP conditions three times, each in separate sessions. K.C.'s second and third test sessions occurred 1

and 8 weeks after the first session, respectively. Thirteen controls (aged 49–61, mean = 54.5) participated once in each condition.

Three stimuli (A,B,C) were used in each of the four conditions. Within each condition, the stimuli were grouped into three completely overlapping pairs (A+ B–, B+ C–, C+ A–). Participants were not informed of any relationship among the stimuli, and were required to use button presses to learn the computerized task by trial and error. Correct responses were rewarded with a happy-face cartoon and the caption “Good Job!!!,” and incorrect responses were followed by an angry-face cartoon and the caption “Wrong!!!.”

RPS was administered first, followed by cards; geometric and abstract stimuli were counterbalanced as third or fourth. Training involved five stages. In Stage 1, participants were presented with 10 trials of each of the problem pairs in consecutive order. Stage 2 consisted of five presentations of each of the pairs in consecutive order. Stage 3 was divided into three blocks and each block was composed of three presentations of each pair in consecutive order. Stage 4 consisted of each problem presented once in consecutive order for nine trials. Stage 5 included two blocks in which each problem was presented 18 times in pseudorandom order. If participants did not obtain an accuracy of 50% correct on any of the training blocks, the block was repeated. Following training, participants underwent a no-feedback test block of twelve trials (four of each pair).

K.C. showed lower training block accuracy on all three sessions than the control group for the abstract and geometric stimuli conditions, revealed by single-sample *t* tests (Crawford and Howel, 1998; Crawford and Garthwaite, 2002; t 's < -2 , P 's ≤ 0.05 ; trend abstract Session 3 and shapes Session 2, $P = 0.07$). In contrast, for the RPS and playing cards conditions, K.C.'s training block accuracy only differed on Session 1 (t 's < -2 , P 's > 0.04), and no differences were detected for Sessions

2 and 3. In addition, K.C. repeated more blocks (due to failure to reach criterion) than the control group for the abstract (Sessions 1 and 2; t 's > 5, P 's < 0.001) and geometric stimuli (Session 1; $t = 3.2$, $P = 0.007$). On the other hand, there were no differences in number of repeated blocks for the RPS or playing cards conditions.

The control group's test block accuracy was ~90% or higher for each pair on every condition, and significantly higher than that expected by chance (t 's > 4.9, P 's < 0.001). K.C.'s test block accuracy for the geometric and abstract stimuli fell below the range of controls' and did not exceed the theoretical maximum of 67% indicative of an elemental strategy (an accuracy of 67% represents successful performance on only two of the three pairs, which can be accomplished using associative learning; Rickard et al., 2006; Fig. 1). Single-sample t tests (Crawford and Howel, 1998; Crawford and Garthwaite, 2002) revealed that K.C.'s accuracy was significantly lower than that of the control group for the geometric and abstract stimulus conditions in all sessions (Table 1). K.C. was also unable to correctly report the relationships among the abstract or geometric stimuli following the experiment.

In contrast, K.C. showed successful TP for RPS in Sessions 2 and 3, with test block accuracy overlapping the confidence interval of the controls, and no significant difference in accuracy from the control group (Table 1). K.C. was able to correctly report the relationship among the RPS stimuli following the experiment. Similarly, for the playing cards, K.C.'s test block accuracy overlapped the control range, nearing the confidence interval, on Session 3, and was well above the 67% elemental theoretical maximum for Sessions 2 and 3. Despite high accuracy levels, K.C.'s accuracy was significantly lower than that of the control group for all three sessions. Interestingly, K.C. was unable to correctly report the relationship among the playing cards immediately following completion of the experiment, as he reported that the "ace" beat both the "king" and the "two."

K.C. showed impaired TP when familiar or unfamiliar stimuli with arbitrary relationships were used. In contrast, he successfully performed TP when familiar stimuli with meaningful relationships were used. K.C. was able to rely upon semantic memories pertaining to RPS and playing cards, as he had played both pre-morbidly, and continues to play cards. Nonetheless, performance on RPS was closest to that of the controls. RPS could possibly be solved with minimal appeal to the relationships among the stimuli by using *a priori* knowledge of the properties of each object, which provide linguistic clues about the relationships among them (scissors cut, rocks crush, paper covers; Hanlon et al., 2005). However, for cards, there were arguably fewer semantic clues as to which choice was correct—specifically, whether the "ace" should be regarded as a "high" or "low" card in each particular pairing. Although K.C. was pre-morbidly familiar with the notion that an ace could function as a high or low card, the specific value of the ace within each particular pairing could not be deduced solely using prior knowledge. That is, prior knowledge could not inform when to treat the ace as a high or low card at any given time. The rule

TABLE 1. Single-Sample t Tests Comparing K.C.'s Test Session Accuracy to That of the Control Group

Condition	t	P
RPS		
Session 1	5.2	0.00
Session 2	0.1	0.26
Session 3	-0.8	0.22
Cards		
Session 1	-7.4	0.00
Session 2	-4.8	0.00
Session 3	-2.2	0.05
Shapes		
Session 1	-5.9	0.00
Session 2	-2.7	0.02
Session 3	-2.9	0.01
Abstract		
Session 1	-4.0	0.00
Session 2	-5.2	0.00
Session 3	-3.7	0.00

"ace > king" and "ace < two" had to be maintained online during performance. K.C.'s performance was likely less accurate than that of the control group, however, because control participants were not limited to online maintenance and could additionally store this rule in long-term memory. K.C. was unable to create a long-term representation of this rule, as he was unable to correctly report the relations among the playing cards immediately following the test session. Nonetheless, K.C. was able to implement known relations flexibly to solve the cards condition, but was unable to learn new relations among the geometric or abstract stimuli. Therefore, amnesia appears to reflect a deficit in the acquisition rather than the processing of relations (Ryan and Cohen, 2004).

We demonstrated successful TP in amnesia using familiar stimuli and relationships. Our findings support those of Rosebaum et al. (2000) and Winocur et al. (2005), which show that performance on a task thought to be reliant on the hippocampus can be mediated by extra-hippocampal structures following extensive pre-morbid experience with the elements of the task and the relations among them. However, our results appear to contradict those of Driscoll et al. (2005) who demonstrated impaired memory for, and reacquisition of, TP following hippocampal lesions. It is possible that the rats in Driscoll et al. (2005) were unable to maintain and reacquire TP performance following hippocampal lesions due to the somewhat limited exposure to the stimuli, and the abstract, arbitrary nature of the TP task employed. Perhaps if given greater pre-morbid experience with the stimuli and their relationships in multiple behavioral contexts, such as in Winocur et al. (2005), some learning could survive hippocampal damage.

We were able to facilitate successful TP in amnesia by encouraging the use of previously acquired semantic relation-

ships, which allowed TP to be solved via extra-hippocampal structures. In essence, tapping previously acquired knowledge renders a situation meaningful. Our work shows that by framing a situation as meaningful we can engage alternate neural systems to compensate for deficient ones.

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REFERENCES

- Alvarado MC, Rudy JW. 1995. Rats with damage to the hippocampal formation are impaired on the transverse-patterning problem but not on elemental discriminations. *Behav Neurosci* 109:204–211.
- Cohen NJ, Eichenbaum H. 1993. *Memory, Amnesia, and the Hippocampal System*. Massachusetts: MIT Press.
- Corkin S. 2002. What's new with the amnesic patient H.M.? *Nat Rev Neurosci* 3:153–160.
- Crawford JR, Garthwaite PH. 2002. Investigation of the single case in neurophysiology: Confidence limits on the abnormality of test scores and test score differences. *Neuropsychologia* 40:1196–1208.
- Crawford JR, Howell DC. 1998. Comparing an individual's test score against norms derived from small samples. *Clin Neuropsychol* 12:482–486.
- Driscoll I, Hamilton DA, Petropoulos H, Yeo RA, Brooks WM, Baumgartner RN, Sutherland RJ. 2003. The aging hippocampus: Cognitive, biochemical and structural findings. *Cereb Cortex* 13:1344–1351.
- Driscoll I, Howard SR, Prusky GT, Rudy JW, Sutherland RJ. 2005. Seahorse wins all races: Hippocampus participates in both linear and non-linear visual discrimination learning. *Behav Brain Res* 164:29–35.
- Driscoll I, Howard SR, Prusky GT, Rudy JW, Sutherland RJ. 2005. Seahorse usus all races: Hippocampus participates in both linear and non-linear visul discrimination learning. *Behav Brain Res* 164:29–35.
- Hanlon FM, Weisend MP, Yeo RA, Huang M, Lee RR, Thoma RJ, Moses SN, Paulson KM, Petropoulos H, Miller GA, Canive JM. 2005. A specific test of hippocampal deficit in schizophrenia. *Behav Neurosci* 119:863–875.
- Moses SN, Ryan JD. 2006. A comparison and evaluation of the predictions of relational and conjunctive accounts of hippocampal function. *Hippocampus* 16:43–65.
- Rickard TC, Grafman J. 1998. Losing their configural mind: Amnesic patients fail on transverse patterning. *J Cogn Neurosci* 10:509–516.
- Rickard TC, Varfaellie M, Grafman J. 2006. Transverse patterning and human amnesia. *J Cogn Neurosci* 18:1723–1733.
- Rosenbaum RS, Priselac S, Kohler S, Black SE, Gao F, Nadel L, Moscovitch M. 2000. Remote spatial memory in an amnesic person with extensive bilateral hippocampal lesions. *Nat Neurosci* 3:1044–1048.
- Rosenbaum RS, Winocur G, Moscovitch M. 2001. New views on old memories: Re-evaluating the role of the hippocampal complex. *Behav Brain Res* 127:183–197.
- Rosenbaum RS, Kohler S, Schacter DL, Moscovitch M, Westmacott R, Black SE, Gao F, Tulving E. 2005. The case of K.C.: Contributions of a memory-impaired person to memory theory. *Neuropsychologia* 43:989–1021.
- Rudy JW, Sutherland RJ. 1995. Configural association theory and the hippocampal formation: An appraisal and reconfiguration. *Hippocampus* 5:375–389.
- Rudy JW, O'Reilly RC. 2001. Conjunctive representations, the hippocampus, and contextual fear conditioning. *Cogn Affect Behav Neurosci* 1:66–82.
- Ryan JD, Cohen NJ. 2004. Processing and short-term retention of relational information in amnesia. *Neuropsychologia* 42:497–511.
- Scoville WB, Milner B. 1957. Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psych* 20:11–21.
- Sutherland RJ, Rudy JW. 1989. Configural association theory: The role of the hippocampal-formation in learning, memory, and amnesia. *Psychobiol* 17:129–144.
- Victor M, Agamanolis D. 1990. Amnesia due to lesions confined to the hippocampus: A clinical-pathologic study. *J Cogn Neurosci* 2:246–257.
- Winocur G, Moscovitch M, Fogel S, Rosenbaum RS, Sekeres M. 2005. Preserved spatial memory after hippocampal lesions: Effects of extensive experience in a complex environment. *Nat Neurosci* 8:273–275.