Published in final edited form as:
J Cogn Neurosci. 2006 October ; 18(10): 1723–1733.

Transverse Patterning and Human Amnesia

Timothy C. Rickard[1], **Mieke Verfaellie**[2], and **Jordan Grafman**[3]
1*University of California, San Diego*

2*Boston University School of Medicine and Boston VA Healthcare System*

3*National Institutes of Health*

Abstract

The transverse patterning (TP) task (A+ B−, B+ C−, C+ A−) has played a central role in testing the hypothesis that medial-temporal (and, in particular, hippocampal) brain damage selectively impairs learning on at least some classes of configural (i.e., nonlinear) learning tasks. Results in the animal and human literature generally support that hypothesis. Reed and Squire [Impaired transverse patterning in human amnesia is a special case of impaired memory for two-choice discrimination tasks. *Behavioral Neuroscience, 113*, 3–9, 1999], however, advanced an alternative account in which impaired TP performance in amnesia reflects a generic scaling artifact arising from the greater difficulty of the TP task compared to the elemental (i.e., linear) control task that is typically used. We begin with a critique of Reed and Squire, countering their conceptual arguments and showing that their results, when analyzed appropriately, support the configural deficit hypothesis. We then report results from eight new amnesic patients and controls on an improved version of the TP task. Despite substantial practice, accuracy of patients with bilateral hippocampal damage due to anoxia reached and maintained an asymptote of only 54% correct, well below the maximum accuracy obtainable (67%) in the absence of configural learning. A patient with selective bilateral damage to the anterior thalamic nuclei exhibited a TP accuracy asymptote that was near 67%, a pattern of two out of three correct consecutive trials, and a pattern of nearly always answering correctly for two of the three TP item pairs. These results are consistent with a set of unique and parameter-free predictions of the configural deficit hypothesis.

INTRODUCTION

Most computation models of medial-temporal amnesia assume that the hippocampal formation has the unique capacity to perform at least some types of nonlinear learning, in which stimulus elements are in some fashion bound, or configured, to represent novel and more complex stimuli (O'Reilly & Rudy, 2001; McClelland, McNaughton, & O'Reilly, 1995; Gluck & Myers, 1993; Sutherland & Rudy, 1989). Direct empirical tests of this *configural learning* hypothesis have come mainly from the animal literature, where the general strategy has been to test normal and hippocampal animals on relatively simple tasks that do or do not require a configural solution. The transverse patterning (TP) task is one prominent example. This task is traditionally introduced in three phases. In Phase 1 of the human version, a single pair of objects (A and B) is presented visually, side-by-side, and the subject must select one of the objects. For this pair, one object (e.g., A) is always correct, regardless of whether it appears to the left or right of B on a given trial. In Phase 2, the (A, B) pair is again presented on half of the trials, and a new pairing (B, C) is presented on half of the trials, with the correct response being B.

Correspondence to: Timothy C. Rickard.

Reprint requests should be sent to Timothy Rickard, Department of Psychology, University of California, San Diego, La Jolla, CA 92093, or via e-mail: trickard@ucsd.edu..

In Phase 3, a third pair (C, A) is added to the mix (correct response is C), so that the subject is presented with (A, B), (B, C), and (C, A), and their reverses, equally often across trials.

Phases 1, 2, and 3 of this problem entail different degrees of reinforcement for each object. In Phase 1, Object A is always reinforced (i.e., is correct) and Object B is never reinforced. In Phase 2, Object A is always reinforced, Object B is reinforced half of the time, and Object C is never reinforced. Because of this monotonically decreasing degree of reinforcement, and thus, response strength, the pairs presented in Phases 1 and 2 are fully solvable by linear learning models (McClelland & Rumelhart, 1986). Standard linear models can never solve Phase 3 of the TP problem completely, however, because in this phase each object is reinforced equally often across trials. Phase 3 of the TP task *can* be solved by a configural learning system that can represent each pair as a new configuration (Rickard & Grafman, 1998; Rudy & Sutherland, 1992, 1994; Sutherland & Rudy, 1989). In most experiments to date, learning on the TP task has been compared with learning on a three-phase control task in which there is no overlap of objects across pairs, as in (D, E), (F, G), and (H, I), and their left–right reversals. All three phases of this control task (often referred to as an elemental learning task) can be solved by a nonconfigural (linear) learning model.

The typical finding in the animal literature is that rats and monkeys with bilateral damage to the hippocampal formation are severely impaired on Phase 3 of the TP task, but not on Phases 1 or 2, nor on any of the three phases of the elemental control task (Alvarado, Wright, & Bachevalier, 2002; Dusek & Eichenbaum, 1998; Alvarado & Rudy, 1992, 1995a, 1995b). Bussey, Warburton, Aggleton, and Nuir (1999) found that fornix lesions did not impair, but actually improved, performance of rats on the TP problem. However, it has since been proposed that the configural learning property of the hippocampus may be mediated by the retrohippocampal or other connection routes (McDonald et al., 1997).

There are other configural tasks that hippocampal animals appear to be able to solve (McDonald et al., 1998, Bunsey & Eichenbaum, 1996; Rudy & Sutherland, 1995; Whishaw & Tomie, 1991), suggesting that the role of the hippocampal formation in configural learning may be circumscribed, although analogous results have not yet been reported for humans. Nevertheless, the data on the TP task suggest that at least some types of configural learning are uniquely performed by the hippocampal formation (for further discussion, see O'Reilly & Rudy, 2001).

Investigation of the TP task was extended to human amnesics by Rickard and Grafman (1998). They studied a group of five human amnesics who had presumed bilateral hippocampal damage resulting from anoxia, hypoglycemia, or ischemia. In accordance with the animal literature, their three densely amnesic patients never solved Phase 3 of the TP task despite as many as 1000 practice trials, whereas all normal control subjects did. All subjects easily solved all phases of the elemental control task.

More recently, however, Reed and Squire (1999) challenged the conclusion that the configural learning requirement of the TP task in Phase 3 is the root cause of the poor performance of amnesic patients. They argued that the impaired TP performance in amnesics instead reflects a scaling artifact related to the more difficult TP task. They reasoned that, because performance of amnesic subjects generally deteriorates with increasing task difficulty, these patients would be expected to have relatively more difficulty learning the TP task (which is more difficult also for controls), even if the hippocampal formation plays no special role in configural learning per se. To test this hypothesis, Reed and Squire first equated difficulty of the TP and elemental control tasks in normal subjects by increasing the number of control pairs that had to be learned. They found that normal subjects required the same number of trials overall to learn the TP and elemental control tasks if the number of elemental control pairs was increased from three to

six (the TP task was left unchanged). They then conducted an experiment similar to that of Rickard and Grafman (1998), but also included this new elemental control condition consisting of six elemental pairs.

Reed and Squire's (1999) patients performed differently than did Rickard and Grafman's (1998) in two respects. First, their patients appear to have learned Phase 3 of the TP task. The sole exception was patient EP, who has severe bilateral medial-temporal damage due to herpes encephalitis, and could not learn either the TP or the control task beyond Phase 1. Second, based on a learning criterion of 14 of 15 consecutive correct trials (the same criterion as used in earlier studies), their patients learned the TP task at the same rate that they learned the six-pair elemental task, but more slowly than they learned the three-pair elemental task. Reed and Squire therefore argued that Rickard and Grafman's results did not reflect selectively impaired configural learning in amnesics, but instead reflected the fact that the TP task is in some unspecified sense more difficult than the three-pair elemental task.

If Reed and Squire (1999) are correct, then their findings necessitate one of two conclusions, either of which could have an important impact on the cognitive neuroscience of amnesia. One possible conclusion, implied by Reed and Squire, is that the hippocampal formation plays no special role in any type of configural processing. Instead, both animals and humans with hippocampal damage are slowed in learning the TP task purely because of an unspecified difficulty factor that is unrelated to the elemental versus configural distinction. Alternatively, one might conclude from Reed and Squire's results that the mnemonic functions of analogous brains regions in humans and animals are highly dissimilar, with the hippocampal formation being selectively involved in at least some types of configural learning for animals but not for humans. Only the results of Rickard and Grafman (1998) for humans appear to be directly at odds with this second conclusion.

A third alternative that we will pursue below is that Reed and Squire's (1999) conclusions are incorrect. We will first discuss methodological and analytical factors which complicate Reed and Squire's interpretation of their data, and we will argue that, when analyzed appropriately, their data converge nicely with those of Rickard and Grafman (1998). We will then present data from a new set of amnesic patients that confirm the findings of Rickard and Grafman and extend the etiologies to include patients with severe bilateral medial-temporal damage due to herpes encephalitis and a patient with rare and selective bilateral damage to the anterior thalamus.

Critique of Reed and Squire (1999)

Reed and Squire (1999) did not include a delay within the third phase of the TP task to test whether their amnesic subjects could retain learning. In contrast, an important aspect of the design of Rickard and Grafman (1998) was that subjects were required to reach the accuracy criterion not just once in their third phase elemental and TP tasks, but again after a delay of at least 1 min that involved casual conversation. Testing after at least a minimal delay may be crucial in evaluating memory deficits because only after a delay can one test for stable long-term memory in the absence of possible working memory confounds. In fact, two of Rickard and Grafman's subjects reached the first learning criterion at least once in Phase 3 of the TP task, but failed to repeat that level of performance after the delay. The simplest integrative account of the results of these two studies is that Reed and Squire's patients, like some of Rickard and Grafman's, achieved some type of unstable, transient solution to the TP task that was not coded into long-term memory.

Although the 14 of 15 consecutive correct trials learning criterion were appropriate in the earlier studies in which there were three pairs for both the TP and elemental tasks, the criterion was not the appropriate measure for comparing learning rates on the TP and three-pair elemental

control tasks on one hand, and the six-pair elemental control task on the other. Consider the results shown in Reed and Squire's Figure 2 (p. 7). The amnesic patients (excluding EP) required an average of 104 trials to learn Phase 3 of the TP task, 49.3 trials to learn the three-pair elemental task, and 105.7 trials to learn the six-pair elemental task. Measured in this way, the six-pair elemental task was indeed about as difficult for the amnesic patients as was the TP task. However, it is clear that the overall number of trials required to reach the 14 of 15 correct criterion will increase markedly with the number of pairs in the stimulus set even if the addition of more items has no negative impact on the trial-to-trial learning rate for each pair (i.e., even if the six-pair task is no more difficult on a per-pair basis than is the three-pair elemental task). As a simplified example, if it takes exactly three repetitions to reach accurate performance for each pair in both the six- and three-pair tasks, then 18 (6 × 3) trials would be required to achieve accurate performance for the six-pair task, whereas only nine (3 × 3) trials would be needed for the three-item task. The appropriate measure of learning rate for the Reed and Squire (1999) experiment is therefore at the pair-level and can be obtained by dividing the total number of trials-to-criterion for each task by the number of pairs used in the task. Transformed in this way, their trials-to-criterion was 34.6 per pair for Phase 3 of the TP task, 16.4 per pair for the three-pair elemental task, and 17.6 per pair for the six-pair elemental task. By this appropriate pair-level learning measure, the learning rates for the three- and six-pair elemental tasks were equivalent and about half that for the TP task. Thus, instead of supporting their generic difficulty hypothesis, Reed and Squire's results actually buttress the configural theory. Increasing the number of elemental control pairs from three to six had no impact on the learning rate, just as the configural theory would predict, provided that interpair interference is minimal (see further discussion of this factor below).

Rickard and Grafman eased their patients into both the TP and elemental control tasks over a series of three phases, using the design outlined earlier. Reed and Squire used the same three phases to introduce the TP task, but for the three- and six-pair elemental tasks they introduced all pairs simultaneously from the outset of practice. This design confound may have artificially decreased the difference in trials to criterion for the elemental and TP tasks.

Reed and Squire (1999) argued that the configural theory may be impossible to test through logical task analysis because it is unclear how the animals treat the stimuli in the configural task. They suggested, for example, that rats might learn a configural problem by simply representing a pair of stimuli as a single object, thus avoiding the need for configuration. However, this interpretation of the configural theory is incorrect, at least for the version specified by Rickard and Grafman (1998). The key point is that the configural system is continually building new configurations out of existing representations of basic stimulus features and of already configured stimuli (both cases can be thought of as elements to be configured in subsequent learning). The theory states that, without the hippocampal structures, there can be no new configurations of these already existing elements. Two or more objects that have never been seen together must be configured through the hippocampal system if those items are to be treated by the animal as a single stimulus. Thus, according to the theory, animals with severe hippocampal damage cannot simply choose to treat two novel stimuli (or two familiar stimuli not seen together before) as a single item to convert the problem into one with an elemental solution.

A final conceptual limitation of Reed and Squire's (1999) approach is that they treated difficulty as a factor to be controlled rather than explained. However, to a large extent, one might describe the constellation of memory tasks on which amnesic subjects are impaired as precisely those tasks that are relatively difficult, where difficulty can be gauged as the potential for interference, either interitem interference within the experiment or interference from preexisting associations (for further discussion, see Rickard & Grafman, 1999; Rudy & Sutherland, 1992, 1994; Kinsbourne & Winocur, 1980). Preferred theoretical approaches provide explicit

computational mechanisms that seek to explain and predict, among other things, why some tasks are more difficult to learn than others.

It may not be possible to conclusively test the configural theory through attempts to equate TP and control tasks for difficulty, when defined in a generic atheoretical way. According to the configural theory as elaborated by Rickard and Grafman (1998), if one added enough new elemental control items to truly equate learning rate per item for the TP and elemental tasks among controls, that effect could occur simply because, with so many elemental pair in the stimulus set, there would be unintended cross-pair interference (due to inevitable overlapping features across objects as the number of pairs grows), in turn requiring as much engagement of the configural system to learn the multipair "elemental" task as for the TP task. Fortunately, there are other unique predictions for the TP task that are open to strong empirical test.

As one example of these predictions, Rickard and Grafman (1998) pointed out that densely amnesic patients can, in principle, achieve a maximum of 67% accuracy on Phase 3 of the TP task, reflecting a linear ordering of response strength among the pairs. If, for example, response strength is highest for Object A and lowest for Object C, then, under idealized circumstances, the subject should always correctly select A for the (A, B) item, always correctly select B for the (B, C) items, but always incorrectly select A for the (A, C) items. Consistent with this prediction, the accuracy level did not consistently exceed this upper bound of 67% for any of Rickard and Grafman's three densely amnesic patients. This quantitative upper bound on performance does not follow from any generic, noncomputational conception of task difficulty. In fact, this parameter-free upper-bound performance prediction appears to follow only from a model that specifies that compromised configural learning is the basis of the amnesic impairment in the TP task. Note, however, that the configural theory does not require that amnesic patients will always perform at this upper-bound accuracy level. As discussed later, there are several factors than may result in poorer performance under some conditions.

Current Experiment

In the following experiment, we sought to better understand performance of human amnesics on the TP task by improving the experimental design, testing a larger number of patients, generalizing over different patient etiologies, and conducting new tests of the predictions of the configural theory. The basic design was similar to that used by Rickard and Grafman (1998), with the primary exception that elemental control and TP pairs were mixed within each of the three phases. This change eliminates one potential confound in the previous studies that does relate indirectly to difficulty; because the TP items are generally more difficult to learn, presentation of these items in a task which is temporally separate from the elemental task, as in previous studies, opens the possibility that subjects might be less motivated for the TP task, in turn worsening performance. By randomly mixing TP and elemental control pairs within each phase in this experiment, subjects cannot anticipate the relative difficulty of the item to appear next, and thus, task-level motivational differences for the two tasks can be eliminated. This design should also reduce residual working memory for earlier presentations of a pair because several pairs intervene between repetitions.

METHODS

Subjects

Eight amnesic patients and eight controls participated in the study. A summary of the patient and control characteristics and neuropsychological findings is given in Table 1. All anoxia patients (Patient 1 [P1] through Patient 5 [P5]) sustained confirmed or presumed (for P2) damage to the hippocampal formation bilaterally. P5 also sustained right amygdala and possible perirhinal damage. P3 also has extensive white matter damage due to multiple

sclerosis. Herpes encephalitis in P6 resulted in bilateral damage to the amygdala, the hippocampus, the perirhinal and entorhinal cortices, the septal region, and the insular cortex (Verfaellie, Koseff, & Alexander, 2000). Herpes encephalitis P7 has bilateral damage to the hippocampus, perirhinal and entorhinal cortices, and to the amygdala. Damage to these structures is virtually complete on the left, with partial preservation on the right. P8 sustained damage bilaterally to the anterior thalamic nuclei due to cerebral infarct.

Materials, Design, and Procedure

Stimuli were nine colored drawings of familiar objects (e.g., car) divided into three groups of three, with one set of three objects constituting the TP stimuli, and the remaining objects constituting the elemental task stimuli, counterbalanced over both controls and amnesics. These stimuli differed from those used by both Rickard and Grafman (1998; simple familiar shapes) and by Reed and Squire (1999; complex, unfamiliar abstract shapes). All stimuli were roughly 2-in. high by 2-in. wide. Subjects were tested in two sessions, each lasting about 40 min, separated by a 30-min rest period. Session 1 began with a Phase 1 study block, which involved presentation of one elemental control pair and one TP pair in an alternating fashion for eight trials, with left–right reversal of the objects on each repetition of an item. On each study trial, the answer was indicated by a flashing red square that framed the correct object and by a message above the correct objects reading “select this one.” The subject then selected the key corresponding to the correct object (the z key if the correct object was on the left, and the / key if the correct object was on the right). The message “correct” then appeared above the object. Next there was a Phase 1 performance block, which was the same as the study block except that the subject had to select the answer rather than having it given to them. If the subject's response was correct, a red square flashed around the selected object, just as in the study phase, and the message “correct” was displayed above the correct stimulus for 2 sec. If the answer was incorrect, the word “Incorrect” flashed, centered at the top of the screen, for 3 sec. Phase 2 study and performance blocks involved presentation of the same pairs as in Phase 1 plus a second pair for both the TP and elemental control tasks. In this phase there were 16 trials (two trials for each pair and its reversal) in both the study and the performance blocks. In the Phase 3 study block, all TP and control pairs and their reversals were presented twice, for a total of 24 study trials. Following the Phase 3 study block, 12 blocks of Phase 3 performance trials were performed to finish out Session 1, where each block had 12 trials (one trial for each of the six pairs and their reversals). Phase 3 pair presentation was random within each block with the constraint that each of the three pairs for each task was presented once in each sequence of three trials for that task. An additional constraint was that a minimum of one trial intervened between repetitions of a pair (i.e., a pair could not be presented both on the last trial of one block and the first trial of the next block). At the end of each block, the computer prompted the experimenter to press the space bar to continue. In Session 2, Phase 3 blocks were repeated until time expired.

RESULTS

All control subjects performed Phases 1 and 2 of the TP and elemental tasks with very few errors. All amnesic subjects learned Phase 1 of both tasks, and performance was generally good on Phase 2 as well. Because there were relatively few trials for those phases, they will not be discussed further.

Average accuracy of control subjects on Phase 3 of the elemental and TP tasks is shown as a function of test block in Figure 1. Control subjects had no difficulty with the elemental control task and learned Phase 3 of the TP task beyond the 67% limit for an elemental learning system, approaching 90% accuracy by the end of the experiment. A linear regression on the mean accuracy data for the TP task revealed a highly significant positive slope [$t(34) = 4.32$, $p < .0001$]. Accuracy was significantly above 67% both on the first [$t(34) = 2.63$, $p = .013$] and on

the last [$t(34) = 10.6$, $p < .0001$] Phase 3 practice block. Control performance on the TP task was somewhat poorer than in previous studies, perhaps because of the interleaving of TP and elemental control items within each block, which may have eliminated any working memory contribution to performance. In any case, these data are consistent with results from numerous studies in the human and animal literature which show that organisms with intact hippocampal structures can learn the TP task.

Performance of amnesic patients on Phase 3 of the elemental control and TP tasks will be described separately for each etiology. Mean accuracy of the five anoxia patients is shown as a function of task and test block in Figure 2. Accuracy on the elemental control task exceeded 90% by the end of Phase 3 practice, and least squares linear prediction of accuracy as a function of practice block confirmed a significant accuracy improvement over trials [$t(1,36) = 2.43$, $p = .02$]. The slower learning of the amnesic patients compared to the control subjects on the elemental task is not in conflict with the configural theory because an intact configural system which can learn quickly could be beneficial for learning both the elemental and TP tasks, and some researchers suggest that humans engage the declarative system—which presumably requires configural learning—by default (e.g., Reed & Squire, 1999).

For the anoxic patients, there was no decrement in accuracy for the elemental task over the 30-min delay between Sessions 1 and 2. On the last three blocks of Session 1, mean accuracy was 0.71, 0.83, and 0.83. On the first three blocks of Session 2, mean accuracy was 0.79, 0.75, and 0.88. This pattern held also for performance of the control subjects on the TP task. These results show that performance was not substantially based on residual working memory for previous repetitions. It appears that working memory has virtually no influence on task performance in a design that mixes together the elemental and TP pairs.

Mean accuracy of the anoxia patients on the TP task was well below the 67% upper bound predicted by the configural theory and improved only minimally with practice (Figure 2). Accuracy did not consistently exceed the 67% boundary for any of the five patients at any point during Phase 3 practice. Linear regression yielded an estimate of 43% correct on the first practice block and 53.8% correct on the last practice block, although the positive slope was not significant [$t(1,34) = 1.74$, $p = .09$]. The trend toward a positive slope reflected primarily the below chance performance by one patient toward the beginning of practice. With that patient removed, the regression slope no longer approached significance ($p = .31$). It therefore appears that these patients reached an asymptotic performance level early in Phase 3 practice, exhibiting no further improvement despite at least 72 repetitions per pair.

These results largely replicate those of the three densely amnesic anoxic patients described in Rickard and Grafman (1998). The current results differ, however, in that no patients ever reached a 14 of 15 consecutive correct trials learning criterion. The mixing of the elemental and TP pairs within the same series of trials in this experiment, which appears to have eliminated any working memory traces of previous exposures to an item, is the most likely factor behind these differing patterns.

Herpes encephalitis P6 failed to learn Phase 3 of either the TP or the control task (Figure 3). His mean accuracies were 0.38 for the control task and 0.57 for the TP task, and there was no trend toward improving accuracy for either task. This result replicates that for Reed and Squire's (1999) patient EP, who also had extensive bilateral medial-temporal damage following herpes encephalitis. These findings indicate that the broader damage sustained by these patients includes areas that are required for timely learning of both the TP and elemental control tasks. This highly intelligent patient scored 141 on the WMS-III working memory scale, further suggesting that working memory was not a factor in task performance.

P7, who uniquely among the amnesic patients had less right- than left-side brain damage, was able to learn both the control and TP tasks to near 100% accuracy by the end of practice (Figure 4). It is possible that the partially preserved right-side structures were sufficient for this patient to perform a TP task on the basis of picture stimuli. Casting some doubt on this interpretation, volumetric analysis indicates that even the right hippocampus in this patient has more atrophy than at least some anoxic patients. It is likely, however, that the level functional deficit is a consequence of both the degree of atrophy and the etiology, and this interaction may be at work. Generally, it seems likely that performance of herpes encephalitis patients, who have highly variable patterns of damage, will be more variable than that of anoxia patients.

P8, who had selective bilateral lesions in the anterior thalamic nuclei, had no difficulty learning the elemental control task and achieved an accuracy of 61.2% on the TP task, higher than that of any of the anoxia patients. To highlight uniquely detailed patterns in this patient's data, each block of 12 trials was divided into two sub-blocks of six trials, each having three elemental task trials and three TP trials. The data in Figure 5 represent these sub-block averages. This patient's TP accuracy improved to 64.2% beyond Block 43, with no further improvement. This plateau effect constitutes striking evidence for a crucial role of the anterior thalamus, which has direct connectivity to the hippocampus, in managing the configural learning requirement of the TP task.

If accuracy of an amnesic patient approaches 67%, as in the case of P8, more specific quantitative predictions fall out of the configural theory. Consider the extreme hypothetical case in which an amnesic patient performs Phase 3 of the TP task with exactly 67% accuracy. As discussed earlier, the only way that an elemental system can achieve this level of performance (reflecting different levels of response strength among elements) is if the patient is always correct on two of three consecutive trials, where each triplet of trials contains one instance of each of the three pairs, as was the case in the experiment. There can be no triplets with zero, one, or three correct trials in this hypothetical case. If we allow for various sources of noise in the data, such as confusion at the motor response execution level, lack of complete stability in the associative structure, and so forth, then accuracy for an amnesic subject will not reach the 67% level (i.e., noise effects alone will tend to yield random performance) and precisely two of three correct trials will not be observed on every triplet.

However, if a subject's accuracy approaches 67%, as for P8, the configural model still makes the unique prediction that the proportion of trial triplets with two out of three correct trials will exceed that expected by a reference model in which there is an equal probability of a correct response on each trial (for the anoxic patients who had TP accuracy near chance, no such effects would be expected, and none were observed). For P8, this reference probability, estimated by his overall accuracy rate, is .612. Given this reference model, the expected proportion (P) of triplets with two out of three correct trials on the basis of chance is $P = 3(x^2)(1 - x)$, where x is the overall accuracy rate (0.607) for the patient.[1] Based on this equation, the predicted value of P is 0.435, whereas P8's actual percentage of triplets with two of three correct trials was 0.83.

To determine the significance of P8's higher rate of two out of three correct, relative to the reference model, a one-way χ^2 test with two categories was performed. The first category represented the predicted (40.1) and observed (78) frequency of triplets on which there were two correct responses. The second category represented the predicted (51.9) and observed (14)

[1]For each of the three possible combinations of two correct and one incorrect trials in a triplet, the probability of two out of three correct for P8 under the reference model is $0.607^2(1 - 0.607) = 0.145$, following the multiplication rule for independent events. Because there are three mutually exclusive combinations of two of three correct trials, the reference probably of two of three correct for a given triplet of trials for P8 is $3 \times 0.145 = 0.435$.

frequency of triplets on which there were no correct responses, one correct response, or three correct responses. The result was highly significant, $\chi^2 = 63.9$, $p < .001$.[2]

The overall percentage correct for trials for P8 beyond Block 43 was 64.2. For these trials, 92.8% of triplets had two of three correct responses, again an extremely significant result, $\chi^2 = 65.4$. Further, for trials beyond Block 43, P8 had an accuracy of 0% on one of the TP pair and of 98.5% and 94.25% for the other two pairs. This result indicates that the same relative response strength order for the three TP objects held throughout practice for this subject once a stable response strength order was achieved.

The finding that only P8 was able to perform very near the 67% accuracy level throughout practice in this experiment suggests that his injury may have impacted the operation of the learning and memory system in a different way than does a hippocampal injury by way of anoxia. We suggest the following preliminary model of the performance differences between the thalamic patient P8 on one hand, and the group of five anoxic patients on the other hand. The core assumptions are that (1) the injury for all of these patients created equivalent impairment of hippocampal function (for the thalamic patient, the impaired hippocampal function is assumed do be indirect via impaired communication between the hippocampus and the thalamus), and thus, of configural functioning for the TP task; and (2) the thalamic injury sustained by P8 further resulted in impaired error correction learning in response to feedback. The hypothesis that the anterior thalamus is critical for error correction learning in response to feedback is plausible given its direct connections to the basal ganglia, another structure that has been implicated in error correction learning (Frank, Seeberger, & O'Reilly, 2004; Lawrence, 2000). The proposal is not that P8 is consciously unaware of error feedback, but rather that the neural connections which might allow for corrective learning as a consequence of feedback are not functional.

If the elemental learning system cannot benefit from feedback, as we hypothesize for the thalamic patient P8, then response strengthening can only occur as a consequence of performance. That is, the only way for P8 to learn would be by associative strengthening for the selected object, regardless of whether that object is correct. Consider the case in which response strength for Object A is the greatest and that for Object C is weakest at some early stage of Phase 3 practice (perhaps due merely to random prior experience biasing the subject toward selecting particular items). Given this initial condition, when the (A, B) item is presented, A will tend to be correctly selected, in turn increasing the response strength for A. When (B, C) is presented, B will tend to be correctly selected, increasing the response strength for B. But when (C, A) is presented, A will always be incorrectly selected. Nevertheless, by hypothesis, response strength for A (but not C) will once again be incremented because the thalamic patient cannot utilize error feedback for corrective learning. Thus, the response strength for A would be reinforced at twice the rate of that for B, and response strength for C should not increase at all with practice. The result would be (1) increasing overall accuracy with practice, approaching but not exceeding 0.67, (2) a substantially above chance proportion of two out of three consecutive correct trials, and (3) very low accuracy for one item along with very high accuracy for the other two items. All of these patterns were observed.[3]

The hypothesis outlined above also leads to two non-intuitive response time (RT) predictions. First, RTs for the (A,C) pair, on which an incorrect response was nearly always made, should be faster than RTs for the other two TP pairs. The reasoning is that there is a greater difference

[2]Because[C2] a parameter of the χ^2 (the expected frequency based on the reference model) was estimated from the data, the standard χ^2 test is not strictly appropriate. However, the probability function for the expected proportion of two out of three correct trials per triplet under the reference model has an upper bound of 0.444 when overall accuracy is 0.667 (it falls as accuracy increases further because the proportion of two out of three correct trials must fall as accuracy increases further). This value of 0.444 was used to perform an auxiliary, worst-case test for the biasing effect of estimating a parameter from the data, yielding a χ^2 of 60.63, $p < .0001$.

in response strength between Objects A and C than between either Objects A and B or Objects B and C (see discussion in the preceding paragraph). Under the reasonable assumption that a greater difference in response strength between objects in a pair translates to a faster RT, the RTs should be fastest for the (A, C) pair. In fact, for the P8's data from Block 44 onward, the mean RT for the (A, C) pair was 1232 msec, whereas the mean RTs for the (A, B) and (B, C) pairs were 1722 and 1633 msec, respectively. In a three-level, one-way analysis of variance (with 69 RT observations per cell), this effect of item was highly significant, [$F(2,204) = 20.2$, $p < .001$]. With the (A, C) pair removed, however, there was no effect [$F(1, 137) < 1.0$]. There were no significant RT effects prior to Block 44, presumably because a stable response strength ordering had not yet been achieved. Second, RTs for the TP pair (A, C) should be faster than mean RT for the elemental control task. By hypothesis, the TP Object A is getting strengthened at twice the rate of the correct (target) objects in the elemental control task (twice per cycle through all items as opposed to once per cycle), and thus, the response strength difference between the objects in TP pair (A, C) should be greater than that for the objects in any of the elemental control pairs. This second RT prediction was also confirmed beyond Block 43. The mean RT for the (A, C) item was 1233 msec, whereas that for the elemental control items was 1372 msec [$F(1,270) = 4.03$, $p = .046$]. Curiously, then, P8 performed fastest on the one pair that he nearly always answered incorrectly. The configural theory makes sense of this finding, whereas it seems unlikely that any alternative theory can.

Now let us consider the anoxia group. Our assumption is that the feedback system is operating normally, but that the configural system is impaired. Thus, on every trial on which the subject makes an error, feedback can result in strengthening of the elemental connection to the correct, nonselected object. The result of this error feedback could be a continuing readjustment of response strength ordering among TP objects, rather than the progressively enhanced separation of response strength ordering that appears to have occurred for the bilateral thalamic P8. Consider again the case of an A > B > C response strength order at a given point in practice. If the (A, C) pair is presented, and the subject incorrectly selects A, feedback can result in an increment in strength for Object C within the elemental learning system. Following sufficient practice, the result of this corrective, feedback-driven associative learning could be that the response strengths of the three objects will tend to converge on the same value, yielding roughly chance performance on each trial. The core underlying assumption here is that, for anoxics, learning from feedback outpaces learning from performance when an error occurs.

DISCUSSION

A goal of this article was to test the ability of the configural theory to capture the performance of human amnesics of different etiologies on the TP task. The results show that patients with select bilateral damage to the hippocampus or the anterior thalamic nuclei cannot learn Phase 3 of the TP task beyond 67% accuracy (the asymptote for an elemental learning system) even after substantial practice. Anoxic patients reached a performance asymptote of about 54% correct early in practice. The bilateral thalamic patient P8 exhibited nearly 67% accuracy on the TP task after some practice and maintained that level of performance, with no further improvements. The thalamic patient P8 also exhibited an emergent pattern of solving two of three consecutive trials correctly and developing a consistent response strength order among TP items during practice. All of these effects follow from or are uniquely consistent with the configural theory of impaired TP performance in amnesia.

[3]According to the impaired feedback processing hypothesis, P8 could also have difficulty learning some elemental pairs if, on initial performance trials, he repeatedly selected the wrong stimulus for a pair, building an incorrect association. Although P8 did make a few errors on the control task during initial Phase 3 performance trials, there was no systematic tendency to make repeated mistakes for a particular item. The study components of Phases 1, 2, and 3 may be important in this respect because they set an environment in which this subject's responses may have been drawn toward a correct stimulus for all elemental pairs prior to his first opportunity to make an error.

The best supported and simplest model of what the hippocampal formation is doing for the TP task is that it is forming fast configurations to assist in solving nonlinear, or configural, problems. For the TP task at least, no other brain system appears to be able to form the configural representations needed to completely learn the task. The conflicting findings of Reed and Squire (1999) are thus best understood as reflecting confounding aspects of their design and analysis, as described earlier. The converging evidence from the numerous human and animal studies now provides a solid empirical foundation for development of models which assume that at least some types of configural learning are selectively impaired in medial-temporal amnesia.

We cannot conclude that learning of the TP task beyond the 67% accuracy boundary is never possible for bilateral hippocampal or anterior thalamic patients with a dense amnesia. One can always argue that insufficient practice was given for patients to acquire a configural solution through slower learning mechanisms in the cortex. Even if that proves to be the case, however, the extended plateau effects at about 64% correct for P8 and at 54% correct for the anoxic subjects in the current study indicate that the hippocampal formation, along with the anterior thalamus, is crucial in providing timely learning of configural information in humans, at least for some types of tasks. These plateau effects may also constitute challenges for recent computational models of animal and human memory functions. O'Reilly and Rudy's (2001) model, for example, predicts that amnesics will have difficulty learning the TP task, but that they will eventually be able to master it through gradual neocortical learning. It remains to be seen, however, whether their model or any other existing model can generate extended accuracy plateau effects at or below the 67% boundary.

It is also instructive to compare the configural theory with the alternative proposal that the hippocampus specializes in encoding memory about relations among objects that can be used flexibly (Eichenbaum, 2000; Cohen & Eichenbaum, 1993). These two theories make two contrasting predictions. First, the configural theory sets forth quantifiable upper performance bounds for amnesic subjects on logically configural tasks, whereas the relational theory specifies no such bounds. Second, the relational theory states that preserved learning in amnesia should be highly brittle, exhibiting little or no flexibility, whereas the configural theory places no such limits on flexible use of memory, beyond those imposed by the impaired configural learning itself. In the human literature, the available evidence supports the configural theory on both counts. In both the Rickard and Grafman (1998) study and the current study, performance of densely amnesic patients on the configural TP task did not exceed the predicted upper bound. Performance of amnesic patients exceeded that upper bound in the Reed and Squire (1999) study, but as noted earlier, there was no delay interval in their design to determine whether that learning reflected stable long-term representation. In a recent study exploring flexibility of preserved memory in amnesia, Bayley, Frascino, and Squire (2005) first taught their subjects an eight-item paired-discrimination task similar to our elemental control task. On a transfer test in which target and distracter objects from the practiced pairs were recombined, accuracy of amnesic patients decreased only slightly, demonstrating memory flexibility of a type that is consistent with configural theory, but inconsistent with the relational theory as developed to date.

In the animal literature, the evidence is more mixed. As noted earlier, animals with hippocampal lesions generally do not learn the TP task, although they do appear to learn at least some other configural tasks. Regarding flexibility of memory, Eichenbaum, Mathews, and Cohen (1989) showed that olfactory discrimination learning in hippocampal rats does not transfer to recombined pairs. Using a visual discrimination task, however, Driscoll, Sutherland, Prusky, and Rudy (2004) obtained perfect transfer to recombined pairs. Driscoll et al. also pointed out that positive transfer to a recombined pair was obtained for an olfactory discrimination task in a study by Dusek and Eichenbaum (1997), and they attributed the impaired transfer observed

by Eichenbaum et al. to different learning strategies of normal and hippocampal rats in that experiment.

An important direction for future work in the human literature is to test amnesics on other learning tasks, such as the biconditional task, that require configural solutions and that hippocampal damaged rats have been shown to learn (e.g., Whishaw & Tomie, 1991). If human amnesics who cannot solve the TP task can solve the biconditional task, then agreement will exist between the human and animal literatures, buttressing models, such as that proposed by O'Rielly and Rudy (2001), that predict serious impairment on the TP task but less impairment on other configural tasks. On the other hand, if human amnesics who cannot learn the TP task also cannot learn other configural tasks, then the configural model remains viable more generally for humans, and important questions would be raised regarding the basis of the differing performance patterns for humans and animals.

Acknowledgments

This research was supported by NIMH Grant #R29 MH58202 to the first author and by NS26985 to Boston University School of Medicine and the Department of Veterans Affairs. We thank Jude Mitchell for programming the experiment and Maria Chi for assistance with data collection.

REFERENCES

Alvarado MC, Rudy JW. Some properties of configural learning: An investigation of the transverse-patterning problem. Journal of Experimental Psychology: Animal Behavior Processes 1992;18:145–153. [PubMed: 1583444]

Alvarado MC, Rudy JW. Rate with damage to the hippocampal-formation are impaired on the transverse-patterning problem but not on elemental discriminations. Behavioral Neuroscience 1995a;109:204–211. [PubMed: 7619311]

Alvarado MC, Rudy JW. A comparison of kainic acid plus colchicine and ibotenic acid-induced hippocampal formation damage on four configural tasks in rats. Behavioral Neuroscience 1995b; 109:1052–1062. [PubMed: 8748956]

Alvarado MC, Wright AA, Bachevalier J. Object and spatial relational memory in adult rhesus monkeys is impaired by neonatal lesions of the hippocampal formation but not the amygdaloid complex. Hippocampus 2002;12:421–433. [PubMed: 12201627]

Bayley PJ, Frascino JC, Squire LR. Robust habit learning in the absence of awareness and independent of the medial temporal lobe. Nature 2005;436:550–553. [PubMed: 16049487]

Bunsey M, Eichenbaum H. Conservation of hippocampal memory function in rats and humans. Nature 1996;379:255–257. [PubMed: 8538790]

Bussey TJ, Warburton EC, Aggleton JP, Muir JL. Fornix lesions can facilitate acquisition of the transverse patterning task: A challenge for “configural” theories of hippocampal function. Journal of Neuroscience 1999;18:1622–1631. [PubMed: 9454867]

Cohen, NJ.; Eichenbaum, H. Memory, amnesia, and the hippocampal system. MIT Press; Cambridge: 1993.

Driscoll I, Sutherland R,J, Prusky GT, Rudy JW. Damage to the hippocampal formation does not disrupt representational flexibility as measured by a novelty transfer test. Behavioral Neuroscience 2004;118:1427–1432. [PubMed: 15598151]

Dusek JA, Eichenbaum H. The hippocampus and transverse patterning guided by olfactory cues. Behavioral Neuroscience 1998;112:762–771. [PubMed: 9733185]

Eichenbaum H. A cortical–hippocampal system for declarative memory. National Review of Neuroscience 2000;1:41–50.

Eichenbaum H, Mathews P, Cohen NJ. Further studies of hippocampal representation during odor discrimination learning. Behavioral Neuroscience 1989;103:1207–1216. [PubMed: 2610913]

Frank MJ, Seeberger LC, O'Reilly RC. By carrot or by stick: Cognitive reinforcement learning in Parkinsonism. Science 2004;306:1940–1943. [PubMed: 15528409]

Gluck MA, Myers CE. Hippocampal mediation of stimulus representation: A computational theory. Hippocampus 1993;3:491–516. [PubMed: 8269040]

Kinsbourne M, Winocur G. Response competition and interference effects in paired-associate learning by Korsakoff patients. Neuropsychologia 1980;18:541–548. [PubMed: 7443017]

Lawrence AD. Error correction and the basal ganglia: Similar computation for action, cognition, and emotion? Trends in Cognitive Sciences 2000;4:1364–1366.

McClelland JL, McNaughton BL, O'Reilly RC. Why are there complementary learning systems in the hippocampus and neocortex: Insights from successes and failures of connectionist models of learning and memory. Psychological Review 1995;102:419–457. [PubMed: 7624455]

McClelland, JL.; Rumelhard, DE. Parallel distributed processing. Explorations in the microstructure of cognition. Volume 1: Foundations. MIT Press; Cambridge: 1986.

McDonald RJ, Murphy RA, Guarraci FA, Gortler JR, White NM, Baker AG. Systematic comparison of the effects of hippocampal and fornix–fimbria lesions on the acquisition of three configural discriminations. Hippocampus 1997;7:371–388. [PubMed: 9287077]

O'Reilly RC, Rudy JW. Conjunctive representations in learning and memory: Principles of cortical and hippocampal function. Psychological Review 2001;108:311–345. [PubMed: 11381832]

Reed JM, Squire LR. Impaired transverse patterning in human amnesia is a special case of impaired memory for two-choice discrimination tasks. Behavioral Neuroscience 1999;113:3–9. [PubMed: 10197901]

Rickard TC, Grafman J. Losing their configural mind: Amnesic patients fail on transverse patterning. Journal of Cognitive Neuroscience 1998;10:509–524. [PubMed: 9712680]

Rudy JW, Sutherland RJ. Configural and elemental associations and the memory coherence problem. Journal of Cognitive Neuroscience 1992;4:208–216.

Rudy, JW.; Sutherland, RJ. The memory-coherence problem, configural associations, and the hippocampal system. In: Schacter, DL.; Tulving, E., editors. Memory systems. MIT Press; Cambridge: 1994.

Rudy JW, Sutherland RJ. Configural association theory and the hippocampal formation: An appraisal and reconfiguration. Hippocampus 1995;5:375–389. [PubMed: 8773252]

Sutherland RJ, Rudy JW. Configural association theory: The role of the hippocampal formation in learning, memory, and amnesia. Psychobiology 1989;17:129–144.

Verfaellie M, Koseff P, Alexander MP. Acquisition of novel semantic information in amnesia: Effects of lesion location. Neuropsychologia 2000;38:484–492. [PubMed: 10683398]

Whishaw IQ, Tomie JA. Acquisition and retention by hippocampal rats of simple, conditional, and configural tasks using tactile and olfactory cues: Implications for hippocampal function. Behavioral Neuroscience 1991;105:787–797. [PubMed: 1777102]

Figure 1.
Mean accuracy of control subjects on Phase 3 of the TP and elemental control tasks as a function of test block.

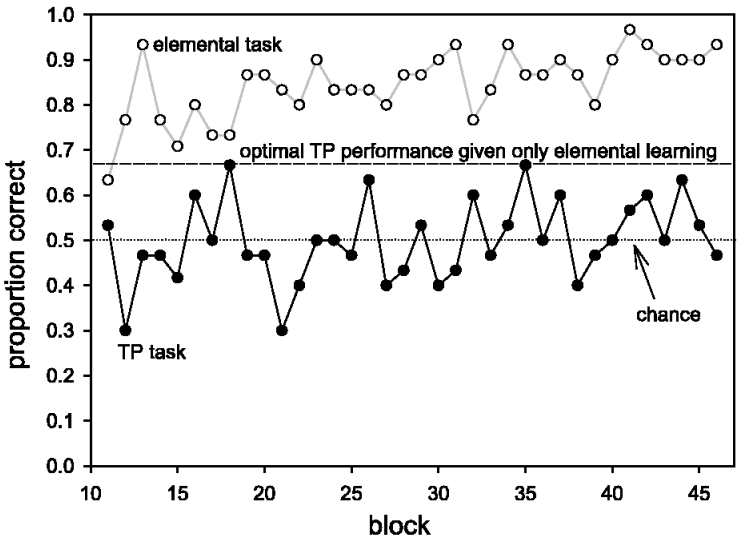

Figure 2.
Mean accuracy of the five anoxia subjects (P1–P5) on Phase 3 of the TP and elemental control tasks as a function of test block.

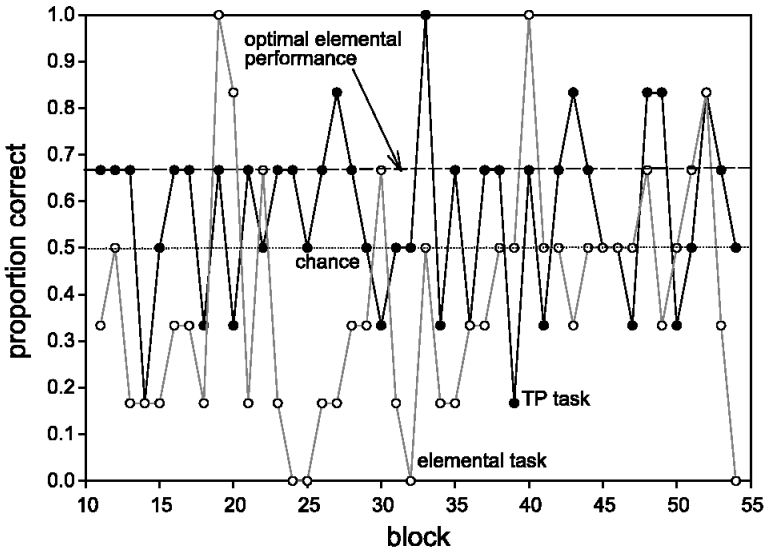

Figure 3.
Mean accuracy of the bilateral herpes encephalitis patient (P6) on Phase 3 of the TP and elemental control tasks as a function of test block.

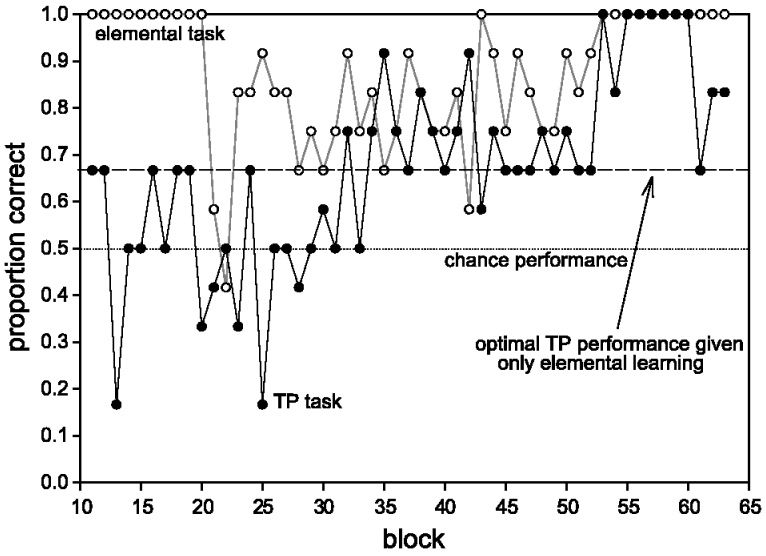

Figure 4.
Mean accuracy of herpes encephalitis patient (P7) on Phase 3 of the TP and elemental control tasks as a function of test block.

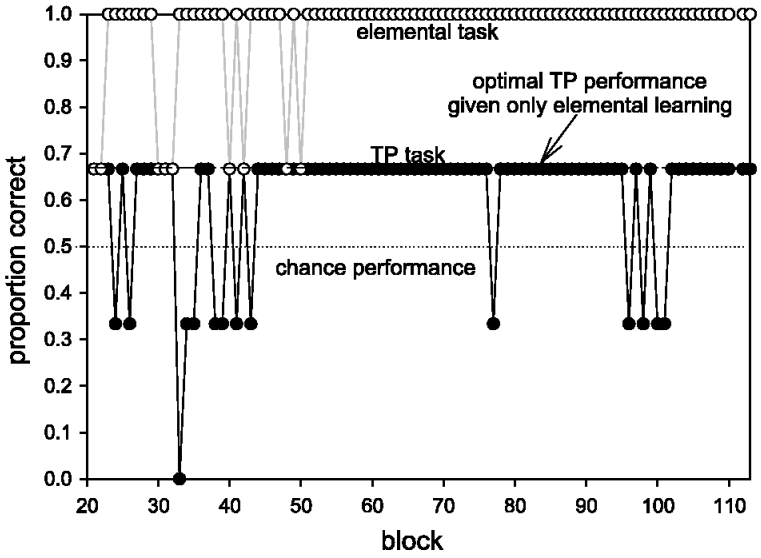

Figure 5.
Mean accuracy of the bilateral anterior thalamic patient (P8) on Phase 3 of the TP tasks as a function of test block.

Table 1

Patient and Normal Control Statistics

Patient ID	*Etiology*	*Age*	*Education*	*VIQ*	*WMS-III*			
					Gen. Mem.	*Aud. Del.*	*Verb. Del.*	*WM*
P1	anoxia	61	16	105	64	58	75	108
P2	anoxia	63	20	111	52	64	56	83
P3	anoxia	50	16	106	47	55	52	99
P4	anoxia	71	18	113	75	80	72	102
P5	anoxia	50	12	83	52	55	56	91
P7	herpes encephalopathy	73	18	135	45	58	53	141
P6	herpes encephalopathy	45	14	92	45	55	56	85
P8	bilateral anterior thalamus	59	12	84	73	67	84	99
Patient means		59	15.7	103.6	58	62.4	62.2	96.6
NC means		59.1	15.6	109.5	—	—	—	—

NC = matched normal control; VIQ = verbal intelligence quotient; Gen. Mem. = general memory; Aud. Del. = auditory delayed memory; Verb. Del. = verbal delayed memory; WM = working memory.