

NEWS AND COMMENTARY

Sequence? What Sequence?: the human medial temporal lobe and sequence learning

Molecular Psychiatry (2003) 8, 896–897. doi:10.1038/sj.mp.4001424

Medial temporal lobe (MTL) dysfunction is well known to impair performance on conscious ‘explicit’ memory tasks, as when people recognize or recall familiar places, people, and events. In contrast, some unconscious ‘implicit’ types of learning and memory have been thought to be independent of the MTL, depending instead on neocortical and various subcortical structures. An implicit learning and memory task can be any perceptual, cognitive, or motor behavior, such as reading or typing, performed without one necessarily being aware of or consciously trying to use memory representations to influence performance with items that had been previously experienced. Implicit learning and memory effects are evidenced as differences (typically improvements) in performance for learned relative to new information.

Convergent findings, especially from studies of human amnesia, have led to explicit–implicit (also declarative–procedural) accounts of learning and memory. By this view, MTL involvement hinges on whether a task requires conscious awareness or intention to learn or remember.¹ However, recent work in animals has begun to cast doubt on the idea that conscious awareness is the primary determinant of MTL involvement.² The findings have instead motivated a ‘relational’ account hypothesizing that the MTL is critically involved in associative processes that bind multiple perceptual, cognitive, and motor aspects of events into a flexible memory trace.³ In contrast to earlier null findings,^{4–8} and favoring a relational view, some recent human neuroimaging and neuropsychological studies suggest that the MTL is necessary also for implicit learning of complex multievent associations.^{9–13}

Our neuroimaging study has provided critical evidence, in particular, that the higher-order associative and temporal structure of the representation being acquired is the primary factor determining recruitment of the human MTL.¹² Furthermore, and contrary to an explicit–implicit account, our findings indicate that the MTL plays a role in learning *regardless* of conscious awareness. Thus, it may be the *nature* of the representation being formed that serves as the primary determinant of MTL recruitment, while a secondary and emergent property of the

representation is its potential accessibility to consciousness.

We acquired fMRI data while individuals performed a serial reaction time task (SRTT), first, without being informed of the presence of an embedded, repeating sequence (implicit experiment), and then a second time, after being informed of and while trying to learn the sequence (explicit experiment). On each trial, one of the four visual locations was cued, and participants pressed a key at the corresponding location. Both experiments included trials of a repeating sequence and of random, novel sequences. Critically, response cues were shown in second-order conditional sequences that entail learning of higher-order associations (at least three consecutive locations within the sequence), not merely simple stimulus–stimulus association pairs, within the repeating sequence. Faster response times (RTs) for repeating relative to random sequences demonstrated higher-order sequence learning. We assessed awareness of the repeating sequence by following both experiments with several tests that probed conscious sequence knowledge. Brain activation that is related to learning a higher-order sequence was assessed by comparing data during repeating vs random sequence conditions.

Our findings provided clear evidence that the hippocampus, adjacent subiculum, and entorhinal and parahippocampal cortices are critical for both implicit and explicit learning of higher-order associations, regardless of sequence awareness. During both implicit and explicit learning, we obtained strong activation in the MTL, as well as in striatal structures implicated in prior neuroimaging studies of implicit learning and dorsolateral prefrontal cortices implicated in studies of explicit learning. Importantly, the MTL activation was not related to awareness, as conscious sequence knowledge was minimal or absent following implicit learning, yet highly accurate following explicit learning. Moreover, we examined fMRI data from the implicit experiment separately for aware vs unaware subgroups (those showing some vs no significant conscious sequence memory), and found that even participants who were unaware of a repeating sequence had significant MTL activation. The fMRI and behavioral results, together, also indicated that learning-related activity in the MTL is related to the acquisition of higher-order associations. Further, we found that MTL activation is strongest during early learning, but diminishes later when fewer higher-order associations remain to be encoded. Overall, our findings indicate that it is the associative

and temporal structure of the mental representation being acquired that is the primary determinant of MTL recruitment.

Our results prompt several important questions in the clinical realm. If the MTL is involved in learning regardless of conscious awareness, what is to be made of findings from neuropsychological studies showing a double dissociation between implicit and explicit learning in patients with basal ganglia vs hippocampal damage? One possible resolution may lie in better understanding the nature of our experimental tasks. Curran reported that amnesic patients with impaired hippocampal systems and intact basal ganglia systems perform normally on the implicit SRTT when assessed by RTs *alone*, but not when gauged by their acquisition of higher-order associations.⁹ Thus, attention should focus on the particular representational demands of the learning experience, regardless of whether the learning mode is implicit or explicit.

In our study, activation was observed in both the MTL and the striatum during sequence learning. This supports the idea that MTL and basal ganglia structures form an interactive memory system,¹¹ which has notable implications for the study of clinical populations. In patients with MTL damage (ie from seizures or Alzheimer's disease) or basal ganglia dysfunction (ie Parkinson's or Huntington's disease, HIV infection), it will be important to examine whether and how the remaining intact system compensates to support learning when the other system is damaged.

In addition, our findings suggest that the hippocampus supports early learning, whereas basal ganglia structures mediate later stages of learning. Thus, it will be important to examine learning across time in individuals with MTL or basal ganglia damage. An example of this was reported in a study of patients with Obsessive Compulsive Disorder, in which only the patients demonstrated sustained activity of the hippocampal system underlying implicit sequence learning, presumably in reaction to dysfunction of striatal regions.¹⁴

Finally, although the current study points to some novel avenues for exploration in the study of human learning and memory, the question still remains—What *is* the precise contribution of the hippocampus in the process of learning? In clinical populations, observations of even subtle differences in the nature of learning in patients with hippocampal dysfunction are likely to aid in addressing this issue. Several

studies have reported decreased hippocampal volumes in individuals with early abuse and long-standing Post-Traumatic Stress Disorder, in addition to dysfunction of the hippocampal system.¹⁵ Examining both the nature of memory formation in the context of immediate trauma, and the impact of hippocampal dysfunction on the ability to form an integrated episodic memory over time may assist in understanding the precise role of the MTL.

Our brain imaging results indicate that the human MTL is involved in sequence learning, regardless of conscious awareness. A person might deny having seen a sequence ('Sequence? What sequence?'), but their MTL has still detected and acquired the temporal order of events. It will thus be essential for future research to consider the role of MTL function in the early acquisition phase of *any* learning paradigm that involves an inherent higher-order associative structure and/or events that evolve over time.

HE Schendan^{1,3}, MM Searl¹, RJ Melrose¹
and CE Stern^{1,2}

¹Center for Memory and Brain,

Department of Psychology, Boston University, USA;

²MGH-NMR Center, Department of Radiology,
Harvard Medical School, USA

³Department of Psychology,

Tufts University, The Psychology Bldg.,
490 Boston Ave., Medford, MA 02155, USA

- 1 Clark RE, Squire LR. *Science* 1998; **280**: 77–81.
- 2 Fortin NJ, Agster KL, Eichenbaum HB. *Nat Neurosci* 2002; **5**: 458–462.
- 3 Cohen NJ, Eichenbaum H. Cambridge, MA: MIT Press, 1993.
- 4 Nissen MJ, Willingham D, Hartman M. *Neuropsychologia* 1989; **27**: 341–352.
- 5 Corkin S. *Neuropsychologia* 1968; **6**: 255–265.
- 6 Knowlton BJ, Ramus SJ, Squire LR. *Psychol Sci* 1992; **3**: 172–179.
- 7 Reber PJ, Squire LR. *Learn Mem* 1994; **1**: 217–229.
- 8 Reber PJ, Squire LR. *J Cogn Neurosci* 1998; **10**: 248–263.
- 9 Curran T. *J Cogn Neurosci* 1997; **9**: 522–533.
- 10 Chun MM, Phelps EA. *Nat Neurosci* 1999; **9**: 844–847.
- 11 Poldrack RA *et al.* *Nature* 2001; **414**: 546–550.
- 12 Schendan HE, Searl MM, Melrose RJ, Stern CE. *Neuron* 2003; **37**: 1013–1025.
- 13 Rose M, Haider H, Weiller C, Buchel C. *Neuron* 2002; **36**: 1221–1231.
- 14 Rauch SL *et al.* *J Neuropsychiatry Clin Neurosci* 1997; **9**: 568–573.
- 15 Pitman RK, Shin LM, Rauch SL. *J Clin Psychiatry* 2001; **62**(Suppl. 17): 47–54.