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Can the hippocampus tell time? The temporo-septal engram shift model

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AN essential feature of episodic memory, the type of memory dependent on hippocampus, is that individual memories belong to particular moments in time. Recent PET studies suggest that memory encoding and recall occur at different locations in human hippocampus. Coupled with other attributes of hippocampus, this suggested to us that the septo-temporal hippocampal axis may play an important role in time perception. We propose a temporo-septal engram shift model of hippocampal memory. The model posits that memories gradually move along the hippocampus from a temporal encoding site to ever more septal sites from which they are recalled. We propose that the sense of time is encoded by the location of the engram along the temporo-septal axis. *NeuroReport* 10:2301–2306 © 1999 Lippincott Williams & Wilkins.

Key words: Computer simulation; Korsakoff; Long-term depression; Long-term potentiation; Memory; Schizophrenia

Introduction

The hippocampus is known to be an important site for the processing of episodic memory. A recent meta-analysis of PET studies of encoding and recall of episodic memory uncovered an unexpected correlation between these two aspects of episodic memory and location of activation along the temporo-septal axis of the hippocampus and hippocampal region [1]. Encoding processes were associated with increased activity in the temporal (anterior) hippocampus while recall tasks produced activity in more septal (posterior) areas. Evoked potential studies have also been consistent with this correlation, showing activation of anterior hippocampus during encoding [2]. The anatomical separation of activity associated with consecutive tasks suggests movement.

The critical feature that serves to define episodic memory, as contrasted with procedural or semantic memory, is that episodes occur at a particular time point. The time of occurrence is therefore an important quality of episodic memory. We propose that this quality is encoded by the movement of the hippocampal representation of the engram along the temporo-septal axis, which we term the temporo-septal engram shift (TSES). In this model, the longitudinal axis of the hippocampus represents a queue where memories, laid down at the temporal (anterior) end, are gradually moved to more septal (posterior) positions. The location of a recalled memory would then provide critical information as to the dating of that memory. We postulate that the time covered by this phenomenon is about 6 months. This is the approximate time during which the hippocampus appears to be involved in human memory [3] and is also about the time for which meaningful estimates of time intervals between episodes can be made [4]. Our prediction is that engrams shift through the temporo-septal axis of the hippocampus during this time period.

Materials and Methods

Computer modeling was done using NEURON [5] on a SUN SPARC20 with vector extensions provided by Z. Mainen. Synapse strengths were calculated using the summed outer-product of all input-output vector pairs. This was then mapped onto a simple Hodgkin-Huxley single-compartment neuronal network model of two 80-unit layers. Parameters were identical to those used in a previous paper [6] with the exception of the following synaptic parameters: GLU: $g = 1$ ns, $C_{dur} = 1$ ms, $\alpha = 1$ mM/ms, $\beta = 0.35$/ms, $E_{syn} = -20$ mV, delay = 0 ms. GABA: $g = 1$ nS, $C_{dur} = 1$ ms, $\alpha = 1$ mM/ms, $\beta = 0.35$/ms, $E_{syn} = -100$ mV, delay = 2 ms.

Results

Previous modeling studies have suggested that individual hippocampal lamellae have the circuitry needed to save sets of memories in a distributed form, using synaptic weight changes to maintain memories [7,8]. In the current study, we suggest that

these memories are shifted, and propose mechanisms whereby this shift might be effected via the majority of fiber tracts which project outside the classic lamella [9]. These extra-lamellar connections would have three functions in this model: (1) shifting memories back through the shift register; (2) retrieval of memories distributed along the longitudinal axis, and (3) determination of the time of the original event relative to the present.

In the temporo-septal engram shift model, the shift of memories to more septal lamellae would be discontinuous and occur during sleep. The rate or frequency of shifting and the number of effective lamellae in the hippocampus will determine the total time stored in the hippocampal queue. Lamellae can be anatomically defined by the thickness of the mossy fiber projection onto CA3, extending about 400 μm longitudinally [10]. Assuming a circadian shift of one such lamella (the diurnal 'growth ring' of hippocampal memory) and a hippocampal length of ~4.5 cm [11], the hippocampus would be expected to store about 4 months of memory, matching other estimates of hippocampal storage duration.

Memory encoding: In order to shift memories temporo-septally during sleep, a wave of activity would have to run in the reverse direction, copying memories out of one lamella before other memories are copied into it. At each location, copying from a source lamella to a destination lamella will involve three steps (Fig. 1A): (1) reactivation of patterns in the source lamella, (2) training of the destination

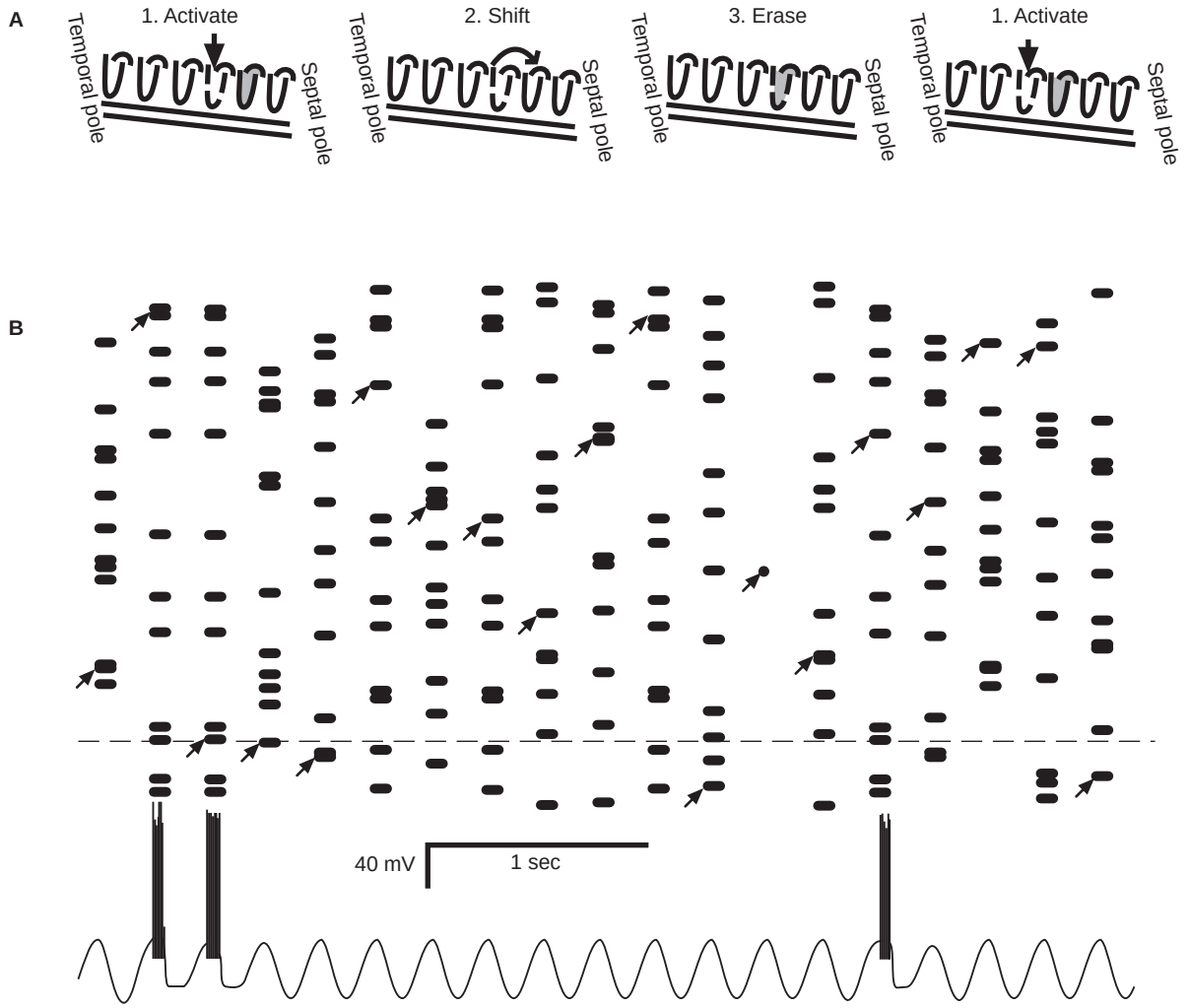

FIG. 1. (**A**) Schematic of the shift process. (**1**) A single lamella is activated by random stimulation (arrow and B). (**2**) Memories are copied onto a previously cleared lamella (cross-hatched). (**3**). The source lamella is erased (cross-hatched). (**1**) Moving temporally, the next lamella is activated. (**B**) Random single cell stimulation elicits full memories in an attractor memory, demonstrating that recall is possible in the absence of content in a content-addressable memory. Raster plot of activity in a 160-neuron bidirectional associative memory (BAM) formed from two reciprocally connected 80-unit heteroassociative memories as described in [6]. Each row shows spike activity in a single neuron. The dashed horizontal line indicates the neuron whose full voltage trace is shown below. Timing of burst firing is determined by a synchronizing theta rhythm introduced into each cell by means of a sinusoidal current injection. Groups of cells are interconnected due to previous Hebbian learning. Cells in a group burst simultaneously following stimulation of one cell in the group (arrow). In most cycles, 14 cells fire, representing one of the stored orthogonal patterns. (A failure occurs on the 13th cycle.) Burst activity terminates both due to the trough of the theta and to delayed feedforward inhibition.

lamella with source lamella patterns using Hebbian learning and (3) erasure of the source lamella so that it can become a destination for more temporally located engrams. We hypothesize that this process would be triggered by a sweep of neural activity, possibly cholinergic or dopaminergic, which would run from septal to temporal pole, consecutively triggering activation of source, Hebbian learning in destination, and erasure of source. The direction of memory shift would be constrained not only by the direction of this sweep, but also by the necessity for specific wiring to permit the transfer, as detailed below.

Step 1, reactivation of patterns, requires that stored memory patterns be retrieved. In general, a weakness of content-addressable memories, as compared to pointer-based memories such as the random-access memory of computers, is that memories are retrieved by their contents and cannot generally be accessed without some notion as to what these contents are. To explore this issue, we constructed a computer model to study random-access memory retrieval in a bidirectional associative memory, a type of content-addressable memory similar in concept to the Hopfield network [12]. We found that increasing connection strength permitted retrieval of memory patterns from progressively smaller memory fragments. At high connection strength, we could retrieve memories from activation of single units (Fig. 1B). Therefore, we suggest that upward modulation of glutamatergic synaptic response coupled with neuronal activation would lead to a rapid sequence of memory repetition. This model is consistent with a previous model used to explain the recapitulation of wake-state firing correlations during sleep [13].

Step 2, copying, could utilize direct longitudinal connections between lamellae to activate corresponding neurons and train connectivity by Hebbian learning. Alternatively, we prefer a model in which memories would be cycled around through subiculum and entorhinal cortex to present them to the destination lamella via the mossy fibers in a form comparable to their presentation in the awake state. Such a copying process would be consistent with the replay of memories in REM [14] or of neuronal correlations in slow-wave sleep [15] and with the memory maintenance hypothesis of Davis, which postulates the need for copying during sleep to avoid memory degradation [16].

Step 3, the process of erasure, would differ biochemically depending on whether long-term potentiation (LTP) of this duration in humans (24 h) is based on protein synthesis as it is in rodents, or on altered levels of protein phosphorylation. Long-term potentiation based on altered phosphorylation levels appears to be reversed by long term depression elicited by maintained low-frequency stimulation. Such a process might occur globally in slow-wave sleep [17], restoring the lamellar *tabula rasa*. Alternatively, individual memory erasure could be effected in our computer model by reducing the feed-forward inhibition that participates in burst termination. This would allow the bursts to extend into the theta trough, producing specific depression of previously potentiated synapses [18].

The repeated rewriting of memories proposed here would provide both advantages and disadvantages for a memory system. A major advantage would be the ability to enrich memories by forming new associations as the memories are replayed. A disadvantage is that movement of memories might be expected to disrupt associations with cerebral cortex. The relationship between hippocampal memory and cortical memory remains uncertain. Two explicit models address this issue. In the memory indexing theory of Teyler and DiScenna, the hippocampus stores pointers that reactivate cortical locations to reproduce a memory [19]. In the consolidation model of Alvarez and Squire, connections between hippocampus and cortex gradually train slower-changing intracortical connections in order to gradually shift memory storage from hippocampus to cortex [20].

Both the memory indexing and consolidation models depend on specific connections between hippocampus and cortex, connections that would be disrupted by movement of memories from one hippocampal location to another. This problem may be moot; it may be that cortex does not make a significant contribution to memory formation until after the hippocampus is done with it. After shifting to the far end of the hippocampus, memory would either be copied to cortex or be lost. However, our model can be reconciled with the memory trace and consolidation models by postulating a multiplexing bus nucleus that would allow any lamella access to cortex [21]. Unlike a computer bus, which is made up of wires that individual microcircuits can tap into, a neural bus would be a nucleus with substantial convergence from different locations. Activation of these cells from any location in the hippocampus would permit subsequent activation of specific areas of cortex. In effect, this bus nucleus would provide hard-wired pointers that the hippocampus could access based on patterns of activation without regard to location.

Recall: Retrieval of stored memories would occur through the processes of pattern completion and pattern convergence that are well characterized in attractor memories [7,8]. Retrieval of information

would be initiated simultaneously in many lamellae, as incoming perceptual signals are broadcast to all lamellae. As recall is initiated, activations would be widespread throughout septal hippocampus reflecting attempted retrieval in different lamellae (see below). The associative memory storage in an individual lamella would respond if the stimulus corresponded to a memory previously stored in that lamella. We assume that the lamellar memory uses the point attractor dynamics of a bidirectional associative memory (BAM). However, the TSES model is consistent with other models of memory storage, such as those dependent on higher dimensional attractors or on transient activity [6].

Lamellar activation would then lead to activation of cortex as suggested by the memory trace and consolidation models, with evocation of cortical zones that represent the sensory, emotional, verbal or cognitive correlates of these memories [21]. The parallel processing of lamellae would allow clear distinctions to be drawn between distinct but similar episodes, something that would be difficult were the memories stored together in a single distributed memory. Individual episodes would retain their identities as separate incidents by being stored separately.

Time of the original event would be retrieved as a partial code based on the location of its engram along the hippocampal axis. By analogy with the auditory time delay system of nucleus laminaris, which transforms time to space, a structure could transform space back into time. The signal coming through a more remote (in time) lamella would reach higher processing centers later than one corresponding to a more recent lamella. This would give one a sense of the flow of time in a speeded-up replay of the past. This model would convert simultaneous, parallel retrieval of memories to a serial presentation for further processing. This would presumably still be preconscious (see below).

Discussion

Over the past century, a large number of models have been proposed to account for the possible underpinnings of remembered time. One simple and intuitively appealing model is the decay or trace-strength model: older memories fade and the degree of fading can be used as a dating of the memory. This can be expressed in physiological terms as a synaptic decay model. With weakening of synaptic input, older memories would be more weakly activated and the absolute strength of response would indicate the age of the memory. Alternatively, and perhaps more reliably, a parallel built-in biochemical decay counter, not part of the memory itself, would affect how it is interpreted by imparting a quality that is interpreted as time. This would act like a carbon-dating of old memories.

The decay counter is one form of a class of model known as time-tag models or encoding models [22]. The simplest of these encodes time by storing the state of one or more putative internal clocks. The most extreme form of this viewpoint, the equivalence postulate, suggests that time can be viewed as another sensory modality that is perceiving the internal clock in much the same way as we perceive the external world through vision or audition. In another variation, encoding occurs as the localization of individual memories in particular slots. Such models depend on depositing memories in order. The original of this model is the century-old conveyor belt model of Guyau [23]. In this model and its many variations [24], memories are laid down in an order that can yield information about sequence and inter-event intervals. The TSES model proposed here is an explicit anatomical version of the conveyor belt or shift register model [25].

Hippocampal circuitry functions: The lamellar hypothesis was originally suggested by *in vivo* physiological results [26]. The functional hippocampal circuitry preserved in the transversely cut hippocampal slice indicates that some hippocampal function can be carried out at the level of the individual lamella [27], even though many pathways are not confined to the lamella [9].

A variety of physiological and anatomical differences have been described along the longitudinal axis of the hippocampus. The source of entorhinal projections to the posterior and anterior regions of the hippocampus differs in the primate, with the lateral entorhinal cortex projecting largely to posterior hippocampus and medial entorhinal cortex projecting to anterior hippocampus [9]. The two regions of the entorhinal cortex may differentially serve encoding and recall with the lateral entorhinal cortex involved in determining temporal aspects of a memory. Similarly, our model is consistent with the hemispheric encoding/retrieval asymmetry (HERA) model [28], the combination of the two models predicting a greater effective connectivity between left frontal cortex and temporal hippocampus (encoding) and between right frontal cortex and septal hippocampus (recall). Place cells, a cellular level correlate of spatial learning in the rat, have been described in both dorsal (septal) and ventral (temporal) hippocampus [29]. The importance of dorsal hippocampus in spatial recall was demonstrated in ablation studies which showed that a large portion of dorsal (septal) hippocampus was required in order to get recall 7 days after learning a water maze task

[30]. In the human, it has also long been noted that amnesic syndromes can occur with ischemic damage in either anterior or posterior temporal lobe [31]. Unfortunately, this damage is typically quite extensive and not restricted to the hippocampus and associated structures.

There are significant differences in wiring and neurotransmitter densities between poles of the hippocampus. These findings suggest a possible division between functionally distinct areas. Anatomically, an increased density of mossy fiber connectivity is seen within dentate gyrus near the temporal pole [32]. The major neuromodulator systems have generally been noted to have their greatest density at the temporal pole, including noradrenergic [33], dopaminergic [34,35] and cholinergic systems [36]. Temporal connectivity and transmitter specializations may be related to the encoding function of this region of hippocampus.

Predictions: The major prediction of this study is that individual memories should be traceable across time from temporal to septal locations in hippocampus. This would seem to be contradicted by the specific results of the PET meta-study, which showed a wide spread of recall-associated activations along much of the longitudinal axis caudal to the posterior commissure [1]. While precise intervals between encoding and recall were not included in the analysis, all but one of the recalls were done within 5–30 min of the encoding. Our hypothesis would thus generally predict that the activations should be clustered near the posterior commissure rather than being so widely scattered. Therefore, while the PET study inspired this model, it also seems to invalidate it.

This apparent contradiction can be reconciled. As noted above, primary initial activation in the septal hippocampal region would be due to simultaneous accessing of all sites in parallel retrieval attempts. Subsequent activations would be due to the retrieval process activating a variety of previous memories throughout the memory queue due to shared attributes that may or may not be related to the specific task being performed. If this is so, the question arises as to why older memories associated with these PET activations are not actively recalled by the person. Perhaps they are; the subjects were not asked to free associate during these tasks. Even if they are not consciously recalled, these activations may well represent the low-level role that the hippocampus plays in recall. Full-blown conscious recall requires activation of many other centers, most notably the frontal and cingulate locations that also activate in PET memory studies [37]. The low-level hippocampal recall may well be promiscuous: the hippocampal memory system casts a wide net and then gives other limbic centers the opportunity to edit a response utilizing the most extensive information available.

It is possible to critically test the current model by designing a PET study utilizing rich, strongly recalled stimuli, as distinct from the minimal word-list or picture stimuli involved in most memory tasks. It is anticipated that there would be enough activity in these engrams to cause measurable metabolic alterations when they are accessed. If events were experienced at different times and then individually evoked at a single later time, the TSES model predicts that these memories (and hence lamellar activations) should be at different places along the temporo-septal axis, with the older memory being localized more septally. Alternatively, memory for a single event recalled at different times should also move along the temporo-septal axis.

Clinical correlates: In the TSES model, movement of memories would be a major source of the internal sense of time passage for intervals of days to months. A variety of insults might be expected to alter this sense. Chief among these would be disruption of paradoxical sleep which might prevent memory shifting. Additionally, drugs that influence the neuromodulators required for the three steps of shifting would also disrupt the sense of time. For example, the flashbacks seen as a sequela of LSD use might be a consequence of a failure of certain memories to be moved out of hippocampal locations indicative of recency. Déjà vu would be experienced if septal lamellae were strongly activated by an input, giving the sense that the input had been experienced before. This could occur as a result of inappropriate activity in a cholinergic or monoaminergic pathway leading to increased sensitivity of one or more lamellae.

A number of clinical syndromes involve alterations in the perception of past time. Korsakoff's syndrome involves damage to the limbic system, resulting in amnesia and inability to store new memories. Anomalies of time concept have been noted in this condition [38]. In contrast to patients with other forms of amnesia, Korsakoff patients have been noted to have particular difficulty placing remembered events in a temporal context. This might again cause confusion between then and now, perhaps contributing to the confabulatory state typical of these patients. Post-traumatic stress disorder is another clinical syndrome characterized by disordered perception of the timing of specific experiences.

Also interesting from a clinical perspective are the opposing effects of D2 and D3 type dopamine

agonists on learning, presumably due to actions in the hippocampus [39]. There is strong pharmacological evidence implicating these receptors in schizophrenia. Temporal disintegration has been noted to be prominent in schizophrenia [40]. A failure of adequate time conveyance or access in the schizophrenic hippocampus could lead to a situation where the time of memory occurrence would be impossible to determine. In particular, this might make it difficult to distinguish recent experiences from more remote experiences, giving past experience an unwonted immediacy. This could be considered the reverse of the déjà vu phenomenon. The occurrence of schizophreniform symptoms in temporal lobe epilepsy [41] may then also be an expression of aberrant activation along the hippocampus.

Conclusion

Previous studies of time perception have generally considered very short time durations, in the order of seconds. Little attention has been paid to longer intervals, whose perception is one aspect of ongoing memory formation and recall. The temporo-septal engram shift model proposes that anatomical localization of the engram along the temporal-septal axis of hippocampus defines the time at which a particular event was encoded into memory. The model thus mediates the mental time travel to the past emphasized by Tulving [42], as activation of that locus by a later event localizes the memory of that event to an appropriate time. Our hypothesis explains an essential feature of episodic memory, the fact that individual memories belong to particular moments in time.

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