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Research report

The temporal attributes of episodic memory

Raymond P. Kesner[a,*], Michael R. Hunsaker[b]

[a] Department of Psychology, University of Utah, Salt Lake City, UT 84112, United States
[b] Program in Neuroscience, University of California, Davis, CA 95616, United States

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ABSTRACT

From a temporal dynamic processing point of view, episodic memory can be divided into three critical time periods: short-term episodic memory with a duration of seconds, intermediate-term episodic memory with a duration from minutes to hours, and long-term or remote episodic memory with a duration from days to years. We propose that short-term episodic memory is mediated by the CA3 subregion of the hippocampus, intermediate-term episodic memory is mediated by the CA1 subregion of the hippocampus (in certain situations aided by the CA3 subregion), and that long-term or remote episodic memory may be mediated by the CA1 subregion. In support of the above mentioned proposal data are presented to support the short-term and intermediate episodic memory functions of CA3 and CA1 based on single item object, spatial location, and object–place association tasks. Additional data are presented for a role for CA3 in short-term episodic memory based on multiple sequential spatial locations, visual objects, and odors tasks. The same episodic memory model based on duration mentioned above cannot easily be applied to the functions of the CA3 (short-term episodic) and CA1 (intermediate-term episodic) for a multiple sequentially presented item, such as a places, objects or odors. The reason for this is that the CA1 region supports, in addition to intermediate episodic memory, temporal pattern separation processes which would reduce interference among sequentially experienced items. The consequence is that this temporal pattern separation process can result in CA1 involvement in short-term episodic tasks based on duration. Also, data are presented based on tasks that involved multiple-trials tested within a day and between days short-term and intermediate-term episodic memory. Furthermore, the mechanisms for understanding the interactions and dissociations between CA3 and CA1 are discussed. The DG appears to have a modulatory influence on the CA3 and CA1 mediation of short-term and intermediate-term episodic memory. The role of CA1 in supporting remote episodic memory requires more experimentation.

1. Introduction

The quest for an animal, and especially rodent, model for episodic memory processing has resulted in a novel outcome measure for lesion as well as transgenic mouse behavioral analyses. To date episodic-like tasks in rodents require "what", "when", and "where" (and in some cases, "which one") components that must be bound into a single behavioral "episode" during encoding to allow for concurrent retrieval of all three elements during the memory test. In this way, the presentation of one of the components would be sufficient to lead to recall of the entire behavioral episode. Much like the research into human episodic memory, these episodic-like memory tasks have implicated the hippocampus as a (if not the) critical locus of episodic-like memory processing.

Unfortunately, this line of inquiry has yet to attempt to parametrize this episodic-like memory processing along the temporal domain. A burning question underlying research into rodent episodic-like memory processing is at what point does a retrieval test actually probe episodic memory and when does the test probe other memory systems that only appear superficially episodic in nature. One way to approach this question is to ask if there are components within the hippocampus, such as the different hippocampal subregions, that underlie separable and dissociable components of episodic-like memory processing. The optimal, albeit naïve, model would be if one could reliably localize the "what" component to the dentate gyrus, the "where" component to CA3, and the "when" component to CA1; thus involving the whole of the trisynaptic loop in the development of an episodic-like memory. This would be countered with memory involving only one or two of the subregions, which would be non-episodic processes.

Although research from our laboratory has not revealed this convenient pattern, research into the dissociable functions of hippocampal subregions have led to a number of potential answers, as well as a mounting number of further inquiries as to the nature of

* Corresponding author at: 380 South 1530 East, Room 502, Salt Lake City, UT 84112, United States. Tel.: +1 801 581 7430; fax: +1 801 581 5481.
E-mail address: ray.kesner@psych.utah.edu (R.P. Kesner).

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how the hippocampus processes behavioral episodes. We suggest that the dentate gyrus is not involved in episodic memory formation per se except in that the separation of similar spatial contexts is essential to recalling one behavioral episode from another (i.e. telling different "where" from each other to prevent false or erroneous episodic recall). The CA3 subregion of the hippocampus is involved in all aspects of episodic memory processing at one point or another, but the involvement of CA3 depends upon the duration of each trial and test session, as well as the interval prior to retrieval of a behavioral episode. The CA1 subregion of the hippocampus is involved in some spatial processing, but primarily CA1 is involved in temporal processing that underlies the temporal separation of behavioral episodes This temporal processing can take the form of processing temporal contingencies during tasks such as trace intervals [48] as well as temporal pattern separation, acting in a manner similar to the dentate gyrus by separating separate temporal contexts (i.e. telling different "when" from each other to prevent false or erroneous episodic recall). These processes are by no means mutually exclusive, but they potentially act via separate mechanisms. Furthermore, the role of CA1 in the temporal processing during any given task may be either in concert with CA3 (via Shaffer collateral input), or may be independent of activity in CA3, depending upon the temporal requirements of the retrieval test.

2. Short-term, intermediate-term, and long-term (remote) episodic memory

From a temporal dynamic processing point of view, episodic memory can be divided into three critical time periods: short-term episodic memory with duration of seconds, intermediate-term episodic memory with duration from minutes to hours, and long-term or remote episodic memory with duration from days to years. It should be recognized that the boundaries between short-term, intermediate-term, and long-term episodic memory are fuzzy and often vary from task to task (Fig. 1). We propose that short-term episodic memory is mediated by the CA3 subregion of the hippocampus, intermediate-term episodic memory is mediated by the CA1 subregion of the hippocampus (in certain situations aided by the CA3 subregion), and that long-term or remote episodic memory is mediated by the CA1 subregion, and fundamentally involves extrahippocampal substrates such as the rostral cortex in rodents or the frontal cortices in humans. These distinctions, although somewhat concretely defined above, are relatively plastic as the design

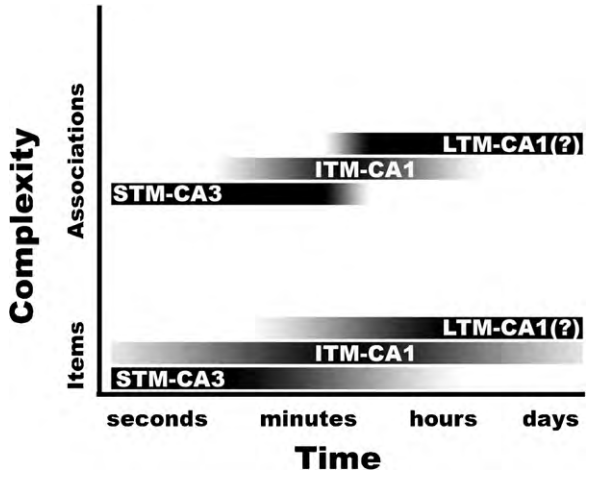

Fig. 1. Temporal organization of short-term episodic memory (STM) supported by CA3, intermediate-term episodic memory (ITM) supported by CA1, and long-term episodic memory (LTM) supported by CA1 based in part on complexity (items, and associations) of information to be remembered.

of the task often can facilitate one type of information processing over another, and some tasks are designed to provide cues that facilitate the use of one brain region over another and can blur the distinctions between the temporal requirements of the task (i.e. free recall vs. recognition memory processing). We propose that CA3 will mediate short-term temporal processing as well as cued-recall and some recognition-memory based processes that facilitate the use of spatial pattern completion over temporal context to solve the task [56,65].

The most extensive data set aimed at addressing the role of the different hippocampal subregions in supporting different temporal frames associated with episodic memory is based in mice and rats. These experiments use paradigms that measure the short-term, intermediate-term, or long-term episodic memory in tasks such as matching or nonmatching-to-sample for single or lists of items, novelty detection based on recognition memory, rapid contextual fear learning, and maze learning. Based on these tasks, it has been suggested that following specific subregional damage, the observation of a complete deficit across all delay intervals implies that the subregion is involved in processing short-term, intermediate-term, and long-term (remote) episodic memory. When there is intact performance at short delays, but impairments at longer delays, the results are interpreted to reflect specific subregional mediation or involvement in intermediate-term or long-term, but not short-term episodic memory. The data that will be presented are primarily based on the subregions of the dorsal hippocampus unless otherwise stated.

3. CA3 vs. CA1 and short-term vs. intermediate-term episodic memory

One of the mnemonic processes suggested for CA3 is to mediate episodic short-term memory via the rapid acquisition of novel information. Marr [46] proposed that the hippocampus should be capable of a rapid formation of simple representations based on modifiable synaptic recurrent collateral associative connections among its neurons (cf. Hopfield [22] for a further characterization of this idea and extension into attractor networks). This idea was further developed by [49,65], who have suggested that, based on CA3 recurrent collateral associative connections, the CA3 system may operate as an attractor network which is useful for some types of short-term episodic memory, including one-trial spatial location, one-trial object, one trial object–place association, one-trial sequential spatial locations, objects or odors, maze learning based on multiple successive trials within a day and fear conditioning based on multiple successive trials within a day.

One of the mnemonic processes suggested for CA1 involves the mediation of temporal processing of information involving chunking and temporally separating information to endow spatial and/or nonspatial contexts with a temporal structure of the information to be remembered (i.e. a temporal context). This process would require extensive processing of information in CA1 and thus may influence intermediate-term, rather than short-term episodic memory representations. If one assumes that CA3 is important for associating, processing, and integrating sequential information, and perhaps for maintaining a short-term episodic representation of sequentially associated information as a context, then this information might be sent via feed-forward connections to CA1 (via the Shaffer collaterals). Computational models and physiological data [65–69] have suggested that CA1 may play a role in compressing temporal sequences. Rolls and Kesner [66] have suggested that CA1 recodes the information represented in the CA3 network by holding one item active in CA3 but continuing firing in an attractor state until the next item in the sequence arrives, when it could be associated with the preceding item by temporally asymmetric synaptic associativity, likely through a chunking process.

This process may be useful for some types of intermediate-term episodic memory, including single item spatial location, object, and object–place associations, multiple items sequential spatial locations, objects or odors, maze learning based on multiple successive trials within a day, and fear conditioning based on multiple successive trials within a day.

4. Short-term and intermediate-term episodic memory for one item

The temporal dynamic processing model that suggests that episodic memory can be divided into three critical time periods, namely short-term episodic memory with duration of seconds, intermediate-term episodic memory with duration from minutes to hours, and long-term or remote episodic memory with duration from days to years as shown in Fig. 1 can be readily applied to the functions of the CA3 (short-term episodic) and CA1 (intermediate-term episodic) for a single item, such as a place, an object, or an object and place association.

4.1. Spatial location

In one study, Lee and Kesner [38] manipulated the NMDA-dependent plasticity in CA3, CA1, or dentate gyrus (DG) by injecting AP5 (a pharmacological antagonist of the NMDA receptors) selectively into CA3, CA1, or DG in a delayed nonmatching-to-place (DNMP) task. During a study phase of the task, rats visited a randomly chosen arm in the 8-arm maze and came back to the center platform where a delay period (10 s) was imposed in a bucket. After the delay period, the rats faced two adjacent arms on the maze (including the arm that had been visited before the delay period) and the task was to choose the arm that had not been visited during the previous study phase. Rats injected with AP5 were not impaired in performing the DNMP task in the familiar environment in which they had been trained. However, AP5 injected into the CA3 initially impaired performance on the task when the same task was carried out in a novel environment (i.e. on a novel maze in a novel testing room). AP5 injected into DG or CA1 did not produce such deficits in the novel environment. Deficits for CA1 emerged when rats were transferred to a 5 min delay. Comparable deficits at a 5 min delay were also found for CA3 lesioned rats. Furthermore, in the same task mentioned above [39]), both lesions of CA3 and transections of CA3 efferents in the dorsal fimbria [27], but not CA1, impaired the acquisition of this task with 10 s delays. At 5 min delays AP5 injections into CA1 produced a sustained deficit in performance, whereas AP5 injections to CA3 did not produce a sustained deficit [38,39]. In a different study, in a delayed matching to sample for a spatial location pattern separation task, requiring episodic short-term memory (in this case a 30 s delay was imposed), it was shown that CA3 lesioned rats were impaired for all pattern separations, consistent with the hypothesis that the rats could not remember the correct spatial location. Furthermore, there were no deficits following CA1 lesions [13].

Using a paradigm developed by Poucet [61], rats with CA3 or CA1 lesions were tested following a 3 min delay between the study and test phases of the task for the detection of a novel spatial configuration of familiar objects. The results indicated that CA3, but not CA1, lesions disrupted novelty detection of a spatial location [36]. Using the same paradigm, with a 3 min delay between the study and test phases, focal injections of diethyldithiocarbamate to produce CA3 lesions in mice resulted in disruption of novelty detection for a spatial location [73]. Based on the idea that the medial perforant path input into the CA3 or CA1 mediates spatial information via activation of NMDA receptors, rats received direct infusions of AP5 into the CA3 or CA1 and were tested for the detection of a novel spatial configuration of familiar objects and the detection of a novel visual object change using the same paradigm mentioned above. The results indicated that AP5 infusions into the CA3 disrupted both novelty detection of a spatial location and a visual object, whereas AP5 infusions into the CA1 disrupted novelty detection of a spatial location, but not the detection of a novel object [24]. In this case, it appears the medial perforant path and the recurrent collateral system in CA3 were either actively maintaining the spatial and nonspatial information as a single behavioral episode in the network over the 3 min intersession interval or else that the rich spatial context available to the rats upon the test session was sufficient to guide retrieval of the previous experience to guide test performance, reflective of episodic processing. CA1, in the absence of recurrent circuitry, appeared to be acting directly upon the spatially rich medial perforant path inputs to retrieve the spatial information needed to perform the test. It is of interest that CA1, as opposed to CA3, did not appear to retrieve the overall behavioral episode in this case to guide retrieval, only the spatial aspects of the experience.

In different research, Lee et al. [42] showed physiologically that plasticity mechanisms in CA3 were activated only when animals encountered novel spatial configurations of familiar cues for the first time. Specifically, rats were trained to circle clockwise on a ring track whose surface was composed of four different textural cues (local cues). The ring track was positioned in the center of a curtained area in which various visual landmarks were also available along the curtained walls. To produce a novel cue configuration in the environment, distal landmarks and local cues on the track were rotated in opposite directions (distal landmarks were rotated clockwise and local cues were rotated counterclockwise by equal amounts). It is well known that principal cells in the hippocampus fire when the animal occupies a certain location of space, known as the "place field" of the cell. Mehta et al. [50] originally showed that the location of the CA1 place field (measured by the center of mass of the place field) changed over time (shifting backward opposite to the direction of rat's motion) in a familiar environment as the animal experienced the environment repeatedly. Such a prominent shift in the place field location appears to be associated with the NMDA dependent plasticity mechanism in the hippocampus [8]. When the rats encountered the changed cue configurations for the first time in Lee et al. [42] experiment, the CA3 place fields shifted their locations backwards prominently compared to the place fields in CA1. However, such prominent shift was not observed in CA3 from day 2 onwards (CA1 place fields started to exhibit a similar property from day 2). This double dissociation in the time course of plasticity between CA1 and CA3 place fields suggests that CA3 reacts rapidly to any changed components in the environment, presumably to incorporate the novel components into an existing episodic short-term memory system or contribute to a new representation of the environment mediated by an episodic short-term memory system if changes are significant. CA1 appears to be performing a similar function, but within an intermediate-term episodic memory system as demonstrated by the different time course than CA3, suggesting that the representation of the behavioral episode in CA1 is processed on a more lengthy timescale than in CA3. Similar results showed that a one-time single lap of short duration across a rectangular track was sufficient to produce enhanced activation of the activity related immediate early gene *Arc* in the CA3, but not the CA1, determined 5 min after the training exposure region [51], suggesting that the CA3, but not CA1, region is associated with a short-term episodic memory. Furthermore, *Arc* in CA1 was recruited after laps across multiple days. At this point it is necessary to point out that the 5 min time point was the time from the behavioral experience to sacrifice of the animal, not a memory duration or intersession interval. The transcription of Arc in CA3 was immediate in this experiment, but was intermediate

in CA1 in that it took multiple experiences and a longer time to experience the new context to initiate this transcription process. These data show the same time course as Lee et al. [42] study with CA3 and CA1 subserving similar functions within different memory systems (short-term vs. intermediate-term episodic memory). Also, in another study it was shown that initial learning of an appetitive operant conditioning task in mice resulted in increased *c-fos* expression in CA3 determined 60 min after the end of the first training session. Furthermore, c-fos was recruited by the second day of training in CA1 [1]. This experiment was studying protein translation, which is not an instantaneous process for c-fos. The 60 min time scale reported is most likely reflective of immediate or very short-term activity in CA3, and the findings during the subsequent day reflect the expanded timescale of CA1 representations.

These data suggest that in some cases CA3 processes information and communicates that information to CA1 via the Schaffer collateral projections. This is similar to a finding from Hampson et al. [17] who recorded ensembles of CA3 and CA1 neurons during a spatial DNMS task. They found cells responsive to spatial location, nonspatial attributes of the task, as well as cells responsive to conjunctions of spatial and nonspatial info (called conjunctive cells in their report). What is of interest is that quite often they found activity in CA1 to be highly correlated to CA3 activity, but later in time, suggesting information transfer from CA3 to CA1. Three neurophysiological and immediate early gene studies suggest the same trend, information being processed by CA3, perhaps in a short-term episodic memory system, and later the same information is coded by CA1, perhaps in an intermediate-term episodic memory system.

4.2. Object

Using a paradigm developed by Poucet [61], rats with CA3 lesions were tested following a 3 min delay between the study and test phases of the task for the detection of a novel visual object change. The results indicated CA3 lesions did not disrupt the detection of a novel visual object change [36]. Using the same paradigm with a 3 min delay between the study and test phases, focal injections of diethyldithiocarbamate to produce lesions in the CA3 region in mice resulted in disruption of novelty detection for a visual object [73]. Based on the idea that the medial perforant path inputs into CA3 mediate visual object information (i.e. "what" information) via activation of opioid receptors, rats received direct infusions of naloxone (a μ opiate antagonist) into CA3 and CA1 and were tested for the detection of a novel spatial configuration of familiar objects and the detection of a novel visual object. The results indicate that naloxone infusions into the CA3 disrupted novelty detection of a spatial location and a visual object, but naloxone injections into CA1 disrupted novelty detection for a visual object, but not for a spatial location [24]. The primary implication of these data is that CA3 is capable of simultaneous processing of both spatial ("where") and nonspatial ("what") elements of episodic memory. This was further characterized by giving AP5 injections into CA3 using the same task. Disruption of either medial perforant path (NMDA-ergic) or lateral perforant path (μ opioid-ergic) plasticity resulted in spatial and novel object detection deficits. In CA1, it appears that the spatial and nonspatial elements are processed separately. Disrupting the lateral perforant path by infusing naloxone was sufficient to disrupt novel object detection, but not sufficient to disrupt detection of a spatial change. Infusing AP5, however, showed the opposite result, a spatial novelty detection deficit without a novel object detection deficit. These data suggest CA3, but not CA1, is critically important for spatial/nonspatial associative binding critical for episodic memory. Similar to the argument provided earlier, it appears that CA3 is involved in rapid spatial and nonspatial information binding into coherent behavioral episodes in the time-scale of this task (each episode is of approximately 6 min duration). When CA3 is disrupted, then the rat fails to retrieve any elements of the episode. This is in contrast to CA1, where it appears that CA1 is involved in temporally tagging information into episodes, and that this is carried out upon each type of information separately (e.g. spatial and nonspatial information), thus a disruption to nonspatial information disrupts only nonspatial processing in CA1.

4.3. Object–spatial location and object–context associations

In the standard model [20,43,46,29,66,67] the CA3 system acts as an autoassociation system. This enables arbitrary (especially spatial in animals and likely language for humans as well) associations to be formed within the hippocampus. The CA3 recurrent collateral associative connections enable bidirectional associations to be formed between whatever stimuli are represented in the hippocampus, in that, for example, any place could be associated with any object, and in that the object could be recalled with a spatial recall cue, or the place with an object recall cue [58,59].

In one ingenious experiment, Day et al. [3] trained rats in a study phase to learn, in one trial, an association between two flavors of food and two spatial locations. During a recall test phase they were presented with a flavor which served as a cue for the selection of the correct location. They found that injections of an NMDA receptor antagonist (AP5) or AMPA receptor antagonist (CNQX) to the dorsal hippocampus prior to the study phase impaired encoding, but injections of AP5 prior to the test phase did not impair place recall, whereas injections of CNQX did impair place recall. The interpretation is that, in the hippocampus, NMDA receptor dependent plasticity is necessary for forming one-trial flavor-place associations, and that recall can be performed without further involvement of NMDA receptors. The reverse order of cuing the location to recall the flavor has not been tested, so that one cannot be sure whether the hippocampus supports arbitrary associations based on this set of experiments.

Based on Day et al. [3] experiment, in the Kesner laboratory a visual object-recall for a spatial location task was developed [33]. In this task, after training to displace objects, rats in the study phase were placed in the start box and when the door in front of the start box was opened the rats were allowed to displace one object in one location, and then after returning to the start box, the door was opened again and the rats were allowed to displace a second object in another location. There were 50 possible objects and 48 locations. In the test phase, the rat was shown one object (first or second randomized) in the start box as a cue, and then, after a 10 s delay, the door was opened and the rats had to go to the correct location (choosing and displacing one of two identical neutral objects). The rats received a reward for selecting the correct location that was associated with the object cue.

A spatial location-recall for a visual object task was also developed. For the spatial-recall for a visual object task, the study phase was the same, but in this case in the test phase, when the door was opened the rat was allowed to displace a neutral object in one location (first or second randomized) on the maze as a location cue, return to the start box, and then, after a 10 s delay, the door was opened and the rats had to select the correct object (choosing and displacing one of two visual objects). The rats received a reward for selecting the correct visual object that was associated with the location cue. Rats learn both tasks with 75% or better accuracy. Results indicate that CA3 lesions produce chance performance on both the one-trial object–place recall and the place–object recall task. The potential implications of such results are that indeed the CA3 supports arbitrary associations as well as short-term episodic memory based on one-trial learning. A control fixed visual conditional to place task with the same delay did not result in an impairment, showing that it was recall after one-trial (or rapid) learning that

was impaired [33]. Additional support comes from the finding that in a similar one-trial object–place learning followed by recall of the spatial position in which to respond when shown the object, Rolls et al. [68] showed that some primate hippocampal (including especially CA3) neurons respond with increased activity in the correct spatial location during and after the recall object cue. Thus, some hippocampal neurons appear to reflect spatial recall given an object recall cue. These data are consistent with the prediction of the standard computational models that emphasizes the importance of CA3 in mediating the development of arbitrary associations. In sum, these results strongly suggest that rapid, plastic changes in the CA3 network are essential for encoding novel information quickly into the hippocampal memory system and NMDA receptor-mediated plasticity mechanisms appear to play a significant role in the process.

There are also a number of studies that have examined the role of the hippocampus in the detection of novelty for changes in object–spatial location, object–context and object–spatial location–context associations based on exploratory behavior. In a number of studies it has been shown that rats can detect a novelty change based on an object–spatial location, object–context experience and object–spatial location–context using an exploratory paradigm with delays between the study and test phase varying from 2 to 105 min. [6,7,53,55]. Even though none of the studies has made subregional lesions of the hippocampus, large hippocampal lesions including dentate gryrus, CA3 and CA1 or fornix lesions do not disrupt the detection of an object–spatial location change [7], but do disrupt an object–context change [7,53,55] and an object–spatial location–context change [7]. Because in the above mentioned exploration tasks, the sample phases and the test phases all operate within a minutes time frame, it is predicted that the CA1 will play an important role in processing object–spatial location–context information.

5. Short-term and intermediate-term episodic memory for multiple items

As stated previously the temporal dynamic processing model that suggests that episodic memory can be divided into three critical time periods, namely short-term episodic memory with duration of seconds, intermediate-term episodic memory with duration from minutes to hours, and long-term or remote episodic memory with duration from days to years as shown in Fig. 1 cannot easily be applied to the functions of the CA3 (short-term episodic) and CA1 (intermediate-term episodic) for multiple sequentially presented items, such as a places, objects or odors. Based on the possibility that newly processed sensory information is organized within the CA1 in such a way to remember and temporarily store one event as separate from another event in time, it can be shown that memory performance improves as the number of items in a sequence between the test items increases, as there may be increased interference for temporally proximal events than temporally distant events [9]. This phenomenon is referred to as the temporal distance effect or temporal pattern separation effect and can be shown to be mediated by the CA1 subregion of the hippocampus. Thus, the CA1 supports both temporal pattern separation and intermediate-term episodic memory. The consequence is that this temporal pattern separation process can result in CA1 involvement in short-term episodic tasks based on duration. For a pictorial representation see Fig. 2.

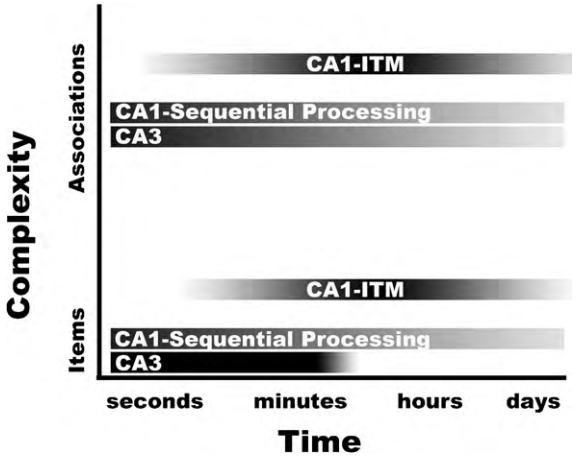

Fig. 2. Temporal organization of short-term episodic memory (STM) supported by CA3, intermediate-term episodic memory (ITM) supported by CA1 based in part on complexity (items, and associations) of information to be remembered. Since temporal pattern separation effects and can be shown to be mediated by the CA1 subregion of the hippocampus, the CA1 supports both temporal pattern separation and intermediate-term episodic memory. The consequence is that this temporal pattern separation process can result in CA1 involvement in short-term episodic tasks based on duration.

5.1. Multiple spatial locations

In order to examine the role of CA3 and CA1, a task was developed in which rats were required to remember multiple places. In the task, during the study phase rats were presented with four different places within sections that were sequentially visited by opening of one door to a section at a time on a newly devised maze (i.e. Tulum maze). Each place was cued by a unique object that was specifically associated with each location within the section during the study phase. Following a 15-s delay and during the test phase, one door to one section would be opened and in the absence of the cued object in that section, rats were required to recall and revisit the place within that section of the maze that had been previously visited. Once animals were able to reliably perform this short-term episodic memory task, they received lesions to either CA3 or CA1. Both CA1 and CA3 lesions disrupted accurate relocation of a previously visited place [37].

In a different task, rats learned trial-unique sequences of spatial locations along a runway box. Each trial consisted of a study phase made up of the presentation of a linear sequence of four spatial locations marked by neutral blocks. After a 30 s interval the animal was given the test phase. The test phase consisted of the same sequence presented during the study phase, but one of the spatial locations was not marked by a block, but still contained a reward. The unmarked spatial location was pseudo-randomly distributed equally between the first, second, third, and fourth item in the sequence. To receive a reward, the rat had to visit the correct, unmarked spatial location. Once animals were able to reliably perform this short-term episodic memory task, they received lesions to either CA3 or CA1. Animals with lesions to either CA3 or CA1 had difficulty with short-term episodic memory processing, although CA1 lesioned animals had a much greater deficit. However, when animals were trained on a non-episodic version of the same task, hippocampal lesions had no effect. These results suggest that CA3 and CA1 both contribute to short-term episodic memory processing, since lesions to CA3 or CA1 result in an inability to process spatial information episodically, whereas they have no effect on non-episodic information processing [28]. Unfortunately, during this task the rats were never tested for retrieval after intermediate or long-term delays. In this case, we attribute the role of CA1 in short-term memory to be due to rapid temporal pattern separation in conjunction with CA3 in that the sequence of spatial locations had severe spatial overlap between trials and was of a very short temporal duration (under 10 s per sample phase). As the post-lesion deficit was greater for the CA1 than the CA3 lesioned group, we

suggest that CA1 was rapidly forming temporal representations for the spatial information from CA3 via the Shaffer collaterals. The nature of this processing was rapid and thus CA1 was drawn into the short-term memory system, but the short-term memory system for temporal information in this case.

In another task Gilbert et al. [14] tested short-term episodic memory for the temporal order of items in a one-trial sequence learning paradigm. In the task, each rat was given one daily trial consisting of a sample phase followed by a test phase. During the sample phase, the animal visited each arm of an 8-arm radial maze once in a randomly predetermined order and was given a reward at the end of each arm. The test phase began immediately following the presentation of the final arm in the sequence. After a 30 s delay in the test phase, two arms were opened simultaneously and the animal was allowed to choose between the two arms. To obtain a food reward, the animal had to enter the arm that occurred earliest in the sequence that it had just followed. Temporal separations of 0, 2, 4, and 6 were randomly selected for each choice phase. These values represented the number of arms in the sample phase that intervened between the two arms that were to be used in the test phase (i.e. a separation of 0 means one arm was presented right after the other). After reaching criterion, rats received CA1 lesions. Following surgery, control rats matched their preoperative performance across all temporal separations. In contrast, rats with CA1 lesions performed at chance across 0, 2, or 4 temporal separations and slightly better than chance in the case of a 6 separation. The results suggest that the CA1 subregion is involved in memory for spatial location as a function of temporal separation of spatial locations since lesions of the CA1 decrease efficiency in temporal pattern separation. CA1 lesioned rats cannot separate events across time, perhaps due to an inability to overcome interference that may be associated with sequentially occurring events. This increase in temporal interference impairs the rat's ability to remember the order of specific events.

Even though CA1 lesions produced a deficit in temporal pattern separation, some computational models [43,44,66,67,79] have suggested that the CA3 region is an appropriate part of the hippocampus to form a sequence memory, for example by utilizing synaptic associativity in the CA3–CA3 recurrent collaterals that has a temporally asymmetric component. It was thus of interest to use the temporal order task to determine whether the CA3 region plays an important role in sequence memory. CA3 lesions impaired the same sequence learning task described above that was also impaired by lesions of the CA1 region [14]. However, this is likely to be the case because of the role of CA3 in processing spatial information.

Thus, short-term episodic memory for multiple places in one-trial multiple place tasks depend on both CA3 and CA1. As an attractor network can generally hold only one item active during a delay period via sustained firing, this type of multiple item short-term memory is computationally predicted to require synaptic modification to store each item as a sequential chunk of information in CA1. As the temporal delays during the study phase and delays before the test in the tasks described above were in the order of seconds, there would also be a requirement for active involvement of CA3.

5.2. Multiple odors

The hippocampus is known to process spatial and temporal information independently [35,57]. In the previous experiments sequence learning and temporal pattern separation was assessed using spatial cues. Therefore, one possibility is that the CA1 and CA3 deficits are due to the processing of spatial rather than nonspatial temporal information. To determine if the hippocampus is critical for processing all domains of temporal information, it is necessary to use a task that does not depend on spatial information. Since the hippocampus does not mediate episodic short-term (delayed match to sample) memory for odors [4,59], it is possible to test whether the hippocampus plays a role in memory for the temporal sequence of odors (i.e. a nonspatial temporal separation effect). Memory for the temporal order of a sequence of odors with a 3 s delay between the study phase and the test phase was assessed in rats based on a varied sequence of five odors, using a similar paradigm described for sequences of spatial locations. Rats with hippocampal lesions were impaired relative to control animals for memory for all temporal distances for the odors, yet the rats were able to discriminate between the odors [32]. In a very similar task developed independently, Fortin et al. [10] reported similar results. In a further subregional analysis, rats with dorsal CA1 lesions show a mild impairment, but rats with ventral CA1 lesions show a severe impairment in memory for the temporal distance for odors [34]. Furthermore, Manns et al. [45] recorded from CA1 pyramidal cells and reported neural activity related to the temporal structure of the sequence in the dorsal/intermediate hippocampus. Thus, the CA1 appears to be involved in separating events in time for both spatial and nonspatial information, so that one event can be remembered distinctly from another event. Interestingly, the dorsal CA1 appears to play a more important role than the ventral CA1 for spatial information [2], and conversely the ventral CA1 appears to play a more important role than the dorsal CA1 for odor information.

5.3. Multiple objects

In order to determine temporal order memory for visual objects, we used a paradigm described by Hannesson et al. [18]. This paradigm involves long duration study phases (on the order of minutes) and long duration tests (also on the order of minutes) for temporal preference and thus is likely to involve more directly the intermediate-term episodic memory processes we have proposed for CA1. In this experiment, rats with CA3 or CA1 lesions were placed inside a box to explore each set of three objects (referred to as A–A, B–B, and C–C) for 5 min with a 3 min inter-session interval. After the third set of objects, the rats were given a 3 min time-out after which one of the two A objects and one of the two C objects were placed in opposite ends of the box. The rats were then returned to the box to measure preference for A vs. C for a 5 min period. On a subsequent day with new objects, the same animals were tested for detection of a novel object as a control using the same procedure previously described with the exception that one of the two A objects and one new object D were placed in opposite ends of the box to measure preference for A vs. D for a 5 min period. All rats were tested once in the A–C preference test (temporal order) and on the A–D preference test (detection of object novelty) for a total of 2 days of testing. The results indicated that CA1 lesions were impaired (they preferred C over A), but CA3 lesioned rats showed the same preference as controls (they preferred A over C). All groups preferred D in the novelty test [21,25]. The data indicate that controls prefer A rather than C. In order to explain this preference for A, it is assumed that rats prefer A because the rat has had more time for consolidation within an intermediate-term episodic memory operation for object A in comparison with object C and thus has greater memory strength for object A. Furthermore, CA1, but not CA3, lesioned rats prefer C suggesting impairments for CA1, but not CA3, in temporal order memory for visual objects. A possible explanation for the observation that CA1 lesioned rats prefer C rather than A is based on the assumption that the trace of A has not been consolidated properly and thus may be difficult to retrieve, but C may still be processed by the short-term episodic memory system mediated by CA3 and thus the rat prefers C because of a short-term recency effect. This would also explain the lack of deficit observed following a lesion of CA3.

Using the same paradigm as described above to examine the effects of dorsal and ventral CA1 lesions on temporal and novelty processing of visual objects, odor, and spatial location information revealed that memory for temporal order information for visual objects is impaired following dorsal and ventral CA1 lesions, for odors following ventral CA1, but not dorsal CA1 lesions, and for spatial locations for dorsal CA1, but not ventral CA1 lesions [21,25]. Thus, CA1 appears to be involved in separating events in time for spatial and nonspatial information, so that one event can be remembered distinctly from another event, but ventral CA1 might play a more important role than dorsal CA1 for odor information. There were no disruptive effects for dorsal or ventral CA1 lesions on novelty detection for odors, spatial locations, and objects [21,25]. It has been shown, however, that lesions to CA3 eliminate any preference for one spatial location over another, suggesting CA3 is also involved in temporal ordering for spatial locations, but only insofar as the information to be temporally processed is spatial in nature.

6. Multiple-trials within a day (encoding) short-term episodic memory and between days (retrieval) intermediate-term episodic memory

In order to test the idea that short-term episodic memory dominates in testing within day and that intermediate-memory episodic memory dominates between days rats with DG, CA3, or CA1 lesions were administered 10 learning trials per day in a Hebb–Williams maze. The results based on a within-day analysis indicated that DG and CA3 lesions impaired the acquisition of this task, consistent with an encoding or learning impairment based on short-term episodic memory [31,41]. However, when tested using a between days analysis, retrieval of what had been learned previously was not impaired by DG or CA3 lesions [31,41]. In contrast, CA1 lesioned animals with lesions to dorsal CA1 show no deficit in encoding, but a significant deficit in retrieval based on intermediate-term episodic memory [76]. In additional experiments CA3 efferents in the fimbria were transected, taking care to spare afferent cholinergic fibers. CA1 efferents in the dorsal fornix were similarly transected. Fimbria transections, but not dorsal fornix transections, resulted in short-term episodic memory encoding deficits during learning of a Hebb–Williams Maze. Dorsal fornix transections, but not fimbria transections, resulted in intermediate-term episodic memory deficits for retrieval of spatial memory after learning a Hebb–Williams Maze. These results suggest that CA3 and CA1 subcortical efferents participate in encoding and retrieval, concordant with the mnemonic role of each subregion [30]. It should be noted that in the Hebb–Williams learning task, one can measure improvement in performance within a day, reflecting the operation of encoding of new information based in part on short-term episodic memory representations and one can also measure improvement in performance between days, reflecting the operation of retrieval of information either based on intermediate-term memory episodic representations mediated by synaptic consolidation and/or access to stored information. It is recognized that the separation of encoding from retrieval processes is extremely difficult. Therefore, it is assumed that during acquisition within a day, there will be a greater involvement of encoding compared to retrieval processes, and that during retention across days, there will be a greater involvement of retrieval compared to encoding processes. It is also assumed that encoding encompasses spatial pattern separation processes in conjunction with associative processes and representations within short-term memory. Even though there is likely to be some retrieval from short-term episodic memory that may also occur during acquisition, it is assumed not to be the dominant factor governing performance within the first 10 trials on Day 1. Furthermore, it is assumed that retrieval 24 h later encompasses associative processes as well as representations within intermediate-term episodic memory. Even though there is likely to be some encoding that may also occur during retrieval, it is assumed not to be the most critical determinant of performance within the first 5 trials on Day 2. In this task, it appears that the contribution of CA3 is to rapidly acquire the spatial relationships to guide proper encoding of an optimal route through space. CA1, on the other hand, appears to be involved in the consolidation/retrieval of this spatial route to guide proper behavior the next day. This could be thought of as a process analogous to retrieving the most recent behavioral experience (that with optimal performance) separate from all others (of more poor performance) to guide performance in the future.

In order to further test the idea that short-term episodic memory dominates in testing within day and that intermediate-memory episodic memory dominates between day, rats with DG, CA3, or CA1 lesions were administered 10 learning trials per day in a contextual fear-conditioning experiment [41]. In this experiment, rats with DG, CA3, or CA1-specific neurotoxic lesions were placed in a contextual fear-conditioning chamber (placed in a room with multiple visual landmarks and distinctive odors as contextual cues). The animals were given a 10 s tone stimulus foot-shock which coterminated with a 2 s foot-shock. When the freezing response was measured during the intertrial interval period during acquisition (when only contextual cues were available), normal animals exhibited freezing behavior from the beginning. In contrast, rats with DG, CA3 or CA1 lesions displayed a delayed onset of freezing behavior, suggesting that rapid formation of memory for the novel contextual cues was disrupted in these animals. However, when tested for retention the next day there was a deficit for DG and CA1 lesioned rats, but no deficit for CA3 lesioned rats. Identical results were reported in a subsequent study [23]. In a different study Daumas et al. [5] used lidocaine injections within CA3 or CA1 prior to acquisition and prior to retention tests. They report a deficit for acquisition, but no deficit for retention, for both CA3 and CA1. The difference in results from the previous two experiments mentioned above might be due to the use of temporary inactivation treatment rather than a more permanent lesion.

In addition to the processing of temporal information, the CA1 subregion appears to have cellular processes that trigger consolidation for new episodic information that are usually completed within minutes and days and thus incorporate intermediate-term episodic memory. One possibility is that CA1 activity promotes the consolidation of new information in the neocortex to use episodic information to build new semantic memories. As mentioned above using a spatial contextual fear conditioning paradigm, rats with dorsal CA1 lesions are relative to controls impaired in retention (intermediate-term episodic memory) of conditioning when tested 24 h following acquisition [40]. Using the same paradigm Hall et al. [15] have demonstrated a relationship between contextual fear memory and the expression of LTP-related immediate early genes (i.e. *BDNF* and *zif268*) in CA1 30 min after the exposure to a contextual fear-conditioning situation. Hall et al. [16] also demonstrated that 30 min following a test for contextual retrieval administered 24 hours after fear conditioning resulted in an increase in *zif268* detected in CA1, suggesting that CA1 was involved in retrieving the memory of the behavioral episode containing the conditioning. Strekalova et al. [72] showed that following a single foot-shock, a test for contextual retrieval 48 hrs later revealed, 90 min later, an induction of *C*-fos and *JunB* early genes in dorsal CA1. No changes were observed in the absence of a test of contextual retrieval. As these early genes containing the cAMP response element (CRE) are essential for gene transcription and protein synthesis after induction of LTP, the enhanced expression of *BDNF* and *zif268*, *C-fos*, and *JunB* also suggests that CA1 is a key subregion for the establishment of intermediate-term memory using cellular consolidation

processes. Support for assigning the above mentioned results to the processing of intermediate-term episodic memory within CA1 comes from the observation that early gene changes in CA1 while observed on day 1 are not observed with longer term retention test at 5 days [16] or 28 days [1]. It is possible that episodic information is processed in neocortex as part of the episodic remote–memory system, in mechanisms similar to those proposed by [47].

7. Interactions and dissociations between CA3 and CA1 in the context of short-term and intermediate-term episodic memory

The dominant view of the relationship between CA3 and CA1 and short-term and intermediate-term episodic memory is that they operate as a feed-forward sequential processing system. The more recent data, however, suggest that, for certain tasks, there are dissociations between short-term vs. intermediate-term episodic memory and between the involvements of the CA3 vs. CA1 subregions. Yet for a different set of tasks both the CA1 and CA3 interact in processing of short-term and intermediate-term episodic memory. Any parallel processing between the CA3 and CA1 would imply possible independence for short-term and intermediate-term episodic memory.

One result that has been obtained when one compares the relationships between CA3 and CA1 is that there is a deficit following dysfunction of the CA3 subregion, but no concomitant deficit following dysfunction of the CA1 subregion. For example, lesions of the CA3, but not the CA1, subregion impair the acquisition of the DNMP task on an 8-arm maze with 10 s delays [39] or novelty detection of a spatial location [36]. Furthermore, CA3, but not CA1, lesions impair within-day learning (encoding) in a Hebb–Williams maze [31,76]. These results suggest that short-term and intermediate-term episodic memory can operate independently of each other. Is there an anatomical basis for this apparent parallel operation between CA3 and CA1 and short-term and intermediate-term episodic memory? Given that CA1 represents the primary output from the hippocampus, especially in light that CA3 does not have direct axonal projections to the subiculum or entorhinal cortex, how can information be transmitted to other neural regions outside the hippocampus once CA1 is ablated? This is very important since other studies have also reported a lack or transient deficit in spatial memory following selective damage to CA1 [52]. One possibility is that outputs that originate from CA3 project via the fimbria directly to the vertical limb of the diagonal band of Broca and medial septum (MS) or indirectly via the lateral septum to MS [12,62,74,75,80]. The vertical limb of the diagonal band of Broca and MS in turn provides cholinergic and GABA-ergic inputs back to the hippocampus, especially the CA3 subregion. These connections have been characterized anatomically via degeneration, fluorescent tracer, and immunohistochemical experiments [12,62,74,75,80]. The connections via the fimbria to the vertical limb of the diagonal band of Broca and MS and especially onto the cholinergic neurons provide an anatomical locus for modulating cholinergic inputs into the hippocampus and especially CA3. An alternate output pathway from the MS to the hippocampus is provided by projections to subiculum and entorhinal cortex, as well as the mammillary bodies. In turn, the mammillary bodies project to the anterior thalamus which projects to entorhinal cortex via the pre- and para-subiculum [78]. There are, therefore, multiple pathways whereby the outputs from CA3 in the fimbria can send information to the entorhinal cortex and subsequently the hippocampus.

In order to examine the hypothesis that the CA3 efferents via the fimbria are involved in acquiring tasks that require learning over multiple trials, the ventrolateral half of the fimbria was transected under electrophysiological control with a retractable wire knife. The rats were then tested in the acquisition of a nonmatch to sample one-trial spatial location task on an 8-arm maze with 10 s delays. Results indicate that fimbria lesioned rats were impaired in acquiring the task similar to CA3 lesioned rats. Furthermore, pairing a CA1 lesion with a fimbria transection mimics the effect of a CA3 lesion, but with longer lasting deficits. In addition, neurophysiological and acetylcholinesterase and BDA (an anterograde tracer) results suggest that the output from dorsal CA3 to the medial septum via the fimbria was damaged without removing the input connections back to dorsal CA3 [29,30]. Furthermore, the same fimbria transection also mimics CA3 lesions in that there is a deficit in the encoding associated with within day learning, but not between day retrieval, in the Hebb–Williams maze and an impairment in detection of spatial novelty [29,30].

One explanation that could provide a mechanism for understanding the fimbria cut induced acquisition deficit is based on the importance of the MS to CA3 connection [74], since even a small disruption to the modulatory cholinergic system could disrupt the ability of CA3 neurons to encode new information [19]. It is assumed that the fimbria output to the MS is excitatory, so that a cut in the fimbria output would result in reduced activation of cholinergic fiber projections, especially to CA3. The consequence of a reduction in the cholinergic influence on the hippocampus could be an increase in the effective strength of the reciprocal, recurrent CA3 connections, which would impair new learning because existing associations in the CA3 to CA3 network would tend to dominate the CA3 cell firing [19]. In this sense, low acetylcholine is appropriate for recall but not for new learning; with low acetylcholine, memories already in CA3 may interfere with setting up new representations in CA3 to be learned. In addition, low acetylcholine after a fimbria cut could impair new learning because long-term potentiation in the CA3 to CA3 synapses is reduced [19]. These acquisition deficits may be especially evident when the task is difficult to learn and requires multiple trials, and interference in encoding of new spatial information becomes more pronounced. Consistent with these hypotheses are observations of Rogers and Kesner [63,64], where they examined the effects of scopolamine injections into dorsal CA3 on the acquisition of the modified Hebb–Williams maze as well as the acquisition of contextual delay fear conditioning. Scopolamine acted to inhibit or reduce encoding or acquisition over multiple trials, but had no real effect on retrieval. The same encoding/retrieval effect was observed for spatial contextual fear conditioning [63]. In another study, Pereira et al. [60] showed that injections of 192 IgG-saporin in the hippocampus, which produced a severe depletion of cholinergic cells in the MS, was sufficient to disrupt the acquisition of the standard Hebb–Williams maze. These data also fit with modeling data indicating that MS innervates CA3 more strongly than CA1 [19] which again emphasizes the role of CA3 in encoding. Another possibility that needs to be considered involves the output route from MS which projects directly to the subiculum and entorhinal cortex or directly to the mammillary bodies and then via the anterior thalamus and pre- and para-subiculum to entorhinal cortex and then hippocampus [78]. It is also possible that the fimbria output may also play a role when after a change in cue configuration the CA3 place fields shifted their locations backwards prominently compared to the place fields in CA1 [42] and when Arc is enhanced in CA3, but not CA1 when a rat is exposed to a single lap in a rectangular track [51]. Furthermore, this double dissociation in the time course of plasticity between CA1 and CA3 place fields suggests that CA3 reacts first to any changed components in the environment presumably to incorporate the novel components into an existing system or build a new representation of the environment if changes are significant.

A second type of result that has been obtained when one compares the relationships between CA3 and CA1 is that there is a deficit following dysfunction of the CA1 subregion, but no con-

comitant deficit following dysfunction of the CA3 subregion. For example, intermediate-term episodic memory in a delayed (5 min) nonmatching-to-sample for a spatial location task is disrupted by AP5 injections into the CA1, but not into the CA3 subregion [38]. Furthermore, temporal order for a visual object [21], retrieval of information acquired in a Hebb–Williams maze [31,76], and retention of contextual fear conditioning are disrupted by CA1, but not CA3 lesions [23,40]. These results also suggest that intermediate-term and short-term episodic memory can operate independent of each other. Is there a different anatomical basis for this apparent parallel operation between CA3 vs. CA1 and short-term vs. intermediate-term episodic memory? In all these cases when there is a deficit following CA1 lesions, but not CA3 lesions, the possibility exists that the deficit is due to a faulty input from the direct perforant pathway to CA1, since the Schaffer collateral input is intact. Based on the idea that in vitro dopamine injections into the CA1 region inhibit the direct perforant path projection to the CA1 region without affecting the Schaffer collateral projection into the CA1 region [58], rats were injected with apomorphine (a nonselective dopamine agonist) or vehicle control in the CA1 region in the delayed (5 min) nonmatching-to-sample for a spatial location task, in the Hebb–Williams maze task, and the contextual fear conditioning task. The results show that apomorphine injections into the CA1 disrupt performance in all these tasks. Furthermore, apomorphine injections into CA1 do not disrupt encoding in the Hebb–Williams maze and transfer of short-term memory for a spatial location in a nonmatching-to-sample task to a novel environment (a new maze) which are processes that are not dependent on the CA1 region [76,77]. Apomorphine injections into the CA1 subregion produces the same pattern of deficits as are produced by CA1, but not CA3, lesions. This result implies that in situations where there is a CA1, but no CA3, lesion effect, the direct perforant path input into the CA1 region represents the main input for the integrity of intact performance perhaps based on intermediate-term episodic memory processing.

A third type of result that has been obtained when one compares the relationships between CA3 and CA1 is that one can observe a deficit following dysfunction of either the CA3 or CA1 subregions. For example, when multiple temporally organized sequential information is to be remembered within a short-term episodic memory system, such as episodic memory for multiple spatial locations both CA3 and CA1 lesions produce impairments [14,28,37]. Thus, there is an implication that both regions are working cooperatively and that CA1 is likely to benefit from a feed-forward Schaffer collateral connection from CA3, but CA1 could also be receiving critical information from the direct perforant path.

In summary, the anatomical organization in terms of afferent and efferent connections of the different subregions of the hippocampus as well as intrinsic operations of each subregion can account for dissociations as well as associations between CA3 and CA1 in supporting short-term and intermediate-term episodic memory, respectively. Thus short-term episodic memory mediated by CA3 and intermediate-term episodic memory mediated by CA1 can operate independent of each other for one set of tasks and interact with each other for a different set of tasks.

8. Dentate gyrus and short-term and intermediate-term episodic memory

The major role of the dentate gyrus is to modulate both short-term and intermediate-term episodic memory via the operation of intrinsic spatial pattern separation processes. There are only a limited number of studies that have examined the influence of spatial pattern separation on short-term and intermediate-term episodic memory. In the first study rats were tested rats with DG lesions using a paradigm that measured short-term memory for spatial location information as a function of spatial similarity between two spatial locations. Specifically, the study was designed to examine the role of the DG subregion in discriminating spatial locations when rats were required to remember a spatial location based upon distal environmental cues and differentiate between the to-be-remembered location and a distractor location with different degrees of similarity or overlap among the distal cues. Animals were tested using a cheeseboard maze apparatus on a delayed-match-to-sample for a spatial location task with 30 s delays and thus can be characterized as a task that requires the operation of short-term episodic memory. Animals were trained to displace an object that was randomly positioned to cover a baited food well in 1 of 15 locations along a row of food wells. Following a short 30 s delay the animals were required to choose between two objects identical to the sample phase object. One object was in the same location as the sample phase object and the second object was in a different location along the row of food wells. An animal was rewarded for displacing the object in the same spatial location as the sample phase object (correct choice) but received no reward for displacing the foil object (incorrect choice). Five spatial separations, from 15 to 105 cm, were used to separate the correct object and the foil object during the choice phase. The results showed that rats with DG lesions were significantly impaired at short spatial separations; however, the performance of the DG lesioned animals increased as a function of increased spatial separation between the correct object and the foil on the choice phases. The performance of rats with DG lesioned matched controls at the largest spatial separation, i.e. there was no deficit at the longest (105 cm) separation even though this task triggers the operation of a short-term episodic memory system. The graded nature of the impairment and the significant linear improvement in performance as a function of increased separation illustrate the deficit in pattern separation and demonstrate that short-term episodic memory is influenced by a pattern separation process [14].

In a second experiment, rats with DG lesions rats were tested in a previously mentioned temporal ordering of spatial location task [26], but in this case with a small distance of 54 or 108 cm at a 30 min delay between the study phase and the test phase consisting of the A vs. C preference test. From a duration model point of view, this task reflects the operation of an intermediate-memory episodic system. The results indicate that animals with DG lesions showed intact preference for A similar to controls with 108 cm spatial separation, but had a deficit in preferring C with a 54 cm spatial separation, suggesting that the DG is involved in intermediate-term episodic memory when there is a difficulty associated with high levels of spatial interference resulting in a spatial pattern separation problem. It appears that a pattern separation process supported by the DG can modulate both short-term and intermediate-term episodic memory.

9. CA1 and remote episodic memory

Remote episodic memory is characterized by prolonged long-term consolidation that can lasts for duration from days to years. There are two major views of the role of the hippocampus and neocortex in subserving remote episodic memory. In the first view new information is encoded in parallel in the hippocampus and neocortex followed by subsequent transfer of information to neocortex (e.g. prefrontal cortex, parietal cortex) [71]. Support for this view comes from the findings of many studies that damage to the hippocampus disrupts short-term and intermediate-term episodic memory rather than remote-term episodic memory [70]. Furthermore, as reviewed by Frankland and Bontempi [11] there are data that support the idea that the prefrontal cortex is directly involved

in remote episodic memory. An alternative view has been proposed by [54]. They formulated a multiple trace theory which suggests that memories are encoded in hippocampal–neocortical networks and that retrieval of remote episodic memories always depend on this hippocampal–neocortical network. Support for this view comes from the findings of a number of studies that damage to the hippocampus can produce an absence of a temporally graded amnesia function. Even though the CA1 may play a role in episodic remote memory, there are no animal data that clearly identify a role for CA1 in either of the above mentioned views of hippocampal involvement in remote episodic memory.

10. Summary

From a temporal dynamic processing point of view, episodic memory can be divided into three critical time periods: short-term episodic memory with a duration of seconds, intermediate-term episodic memory with a duration from minutes to hours, and long-term or remote episodic memory with a duration from days to years. We propose that short-term episodic memory is mediated by the CA3 subregion of the hippocampus, intermediate-term episodic memory is mediated by the CA1 subregion of the hippocampus (in certain situations aided by the CA3 subregion), and that long-term or remote episodic memory may be mediated by the CA1 subregion. In support of the above mentioned proposal data are presented to support the short-term and intermediate episodic memory functions of CA3 and CA1 based on single item object, spatial location, and object–place association tasks. Additional data are presented for a role for CA3 in mediating short-term episodic memory based on multiple sequential spatial locations, visual objects, and odors tasks. The same episodic memory model based on duration mentioned above cannot easily be applied to the functions of the CA3 (short-term episodic) and CA1 (intermediate-term episodic) for a multiple sequentially presented item, such as a places, objects or odors. The reason for this is that the CA1 region supports, in addition to intermediate episodic memory, temporal pattern separation processes which would reduce interference among sequentially experienced items. The consequence is that this temporal pattern separation process can result in CA1 involvement in short-term episodic tasks based on duration. Also, data are presented based on tasks that involved multiple-trials tested within a day and between days short-term and intermediate-term episodic memory. Furthermore, the mechanisms for understanding the interactions and dissociations between CA3 and CA1 are discussed. The DG appears to have a modulatory influence on the CA3 and CA1 mediation of short-term and intermediate-term episodic memory. The role of CA1 in supporting remote episodic memory requires more experimentation.

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