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REVIEW

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Hippocampal function in cognition

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Abstract *Rationale and objectives:* Any consideration of cognitive disruption in schizophrenia quite naturally leads to questions concerning the cellular and molecular mechanisms underlying normal cognition. This review will describe emerging models for the cellular basis of cognitive processing in the hippocampus. *Methods and results:* This review will describe results from several laboratories that have used in vivo recording in behaving rodents to probe the role of the hippocampus in cognition. These exciting studies have indicated a broader role of the hippocampus in general information processing than was previously appreciated. These recent results suggest that the hippocampus is involved in minute-to-minute cognitive processing including spatial information processing, temporal sequencing, and formulating the relationships between objects in the environment. *Conclusions:* The hippocampus appears to play a major role in bringing together environmental signals and producing a cohesive and unified percept in the spatial and temporal domains. This new view of the role of the hippocampus in cognition fits strikingly well with models for schizophrenia hypothesizing hippocampal dysfunction as one cause of cognitive decline in schizophrenic patients.

Keywords Learning · LTP · Memory · Place cell · Hippocampus · Schizophrenia

This review covers recent advances concerning the cellular and molecular mechanisms involved in hippocampus-dependent memory formation. Why is a review in this area included in an issue of *Psychopharmacology* devoted to cognitive dysfunction in schizophrenia? The answer is not simple. One consideration is that mechanisms of learning and memory are integral to cognition, and this fact in itself is a compelling reason for including a review on hippocampus-dependent memory formation in a compilation of articles on cognition and schizophrenia. However, in my opinion that is not the most compelling reason for including a review on recent advances in understanding hippocampal function in cognition in this special issue. The more substantial motivation likely comes from considering new, emerging models for the role of the hippocampus in real-time information processing.

It is becoming clear that the hippocampus is involved in much more than just its well-established role in long-term memory consolidation. Experimental results over the last several years have demonstrated that the hippocampus is involved in moment-to-moment processing of a wide variety of environmental signals and in forming a cohesive construct and unified representation of the outside world within the central nervous system (CNS). This new understanding has emerged largely from studies of hippocampal pyramidal neuron firing patterns recorded in vivo in behaving rodents, studies that will be emphasized in this review. Thus, I will describe work from several laboratories that followed the patterns of firing of hippocampal pyramidal neurons while animals executed a number of different behavioral tasks, including exploring mazes, learning that some environmental cues reliably predict others, and while processing complex environmental signals. These studies have led to a new appreciation of the role of the hippocampus in moment-to-moment cognitive processing, and in forming a cohesive construct of the animal's surround.

The studies providing the basis for this emerging model of hippocampal function have been carried out in parallel with, and unbeknownst to, most schizophrenia researchers. The converse is also the case—most investigators interested in the basic biology of cognition do not appreciate the emerging emphasis among schizophrenia researchers on cognitive dysfunction in their patient population of interest. The principal motivation for this review is to begin to provide a bridge between basic

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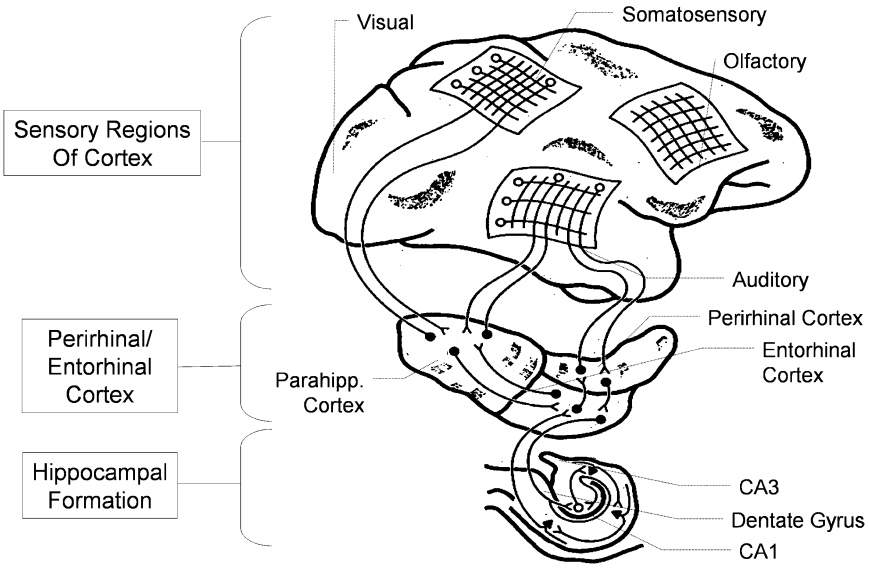

Fig. 1 Hippocampal connectivity in the central nervous system. Illustration of the pathway from sensory regions of the cortex through the perirhinal and entorhinal cortices to the hippocampal formation. Figure adapted from Squire and Zola-Morgan (1991) (copyright American Association for the Advancement of Science)

researchers interested in cognition and those interested in schizophrenia, by drawing attention to the complementary nature of recent ideas on the role of the hippocampus in cognitive processing with recent models for cognitive dysfunction in schizophrenia.

This review will emphasize three new areas of discovery in studies of the hippocampus in order to illustrate this point. First, it has become clear that the hippocampus is involved in creating a cognitive construct of the space surrounding an animal. This is illustrated by the firing patterns of hippocampal pyramidal neurons referred to as place cells, which reliably fire when an animal perceives itself to be in a particular location in a maze or open field that it has explored. Second it also has become clear that the hippocampus is involved in processing temporal relationships between stimuli and in creating a construct of the ordering of events. This is illustrated by considering the firing of hippocampal neurons when an animal is learning contingencies, such as in a Pavlovian associative learning task where one cue predicts that another will follow after a set time interval. Finally, the hippocampus is involved in correctly binding together a unified construct of the relationships of objects in the environment with each other. This will be illustrated by considering hippocampal neuron firing patterns when an animal learns that objects in its environment can predict one thing in one circumstance and something different when the animal's recent history is different.

These three new areas of hippocampal function in cognition will be organized under the rubric space, time, and relationships. This is in order to provide a convenient organizing nomenclature for new models of hippocampal function that are emerging from animal studies. Nevertheless, these emerging roles for the hippocampus in general cognition are strikingly reminiscent of the spectrum of cognitive disorders observed in schizophrenic patients.

These various cognitive functions of the hippocampus are in addition to the well-established necessity for hippocampal function in long-term memory consolidation, which will also be considered briefly. I should point out before proceeding further that I have explored these ideas in much greater detail in a recent book, *Mechanisms of Memory* (Sweatt 2003), and that parts of this review are a distillation from that book.

The organization of this review is as follows. First, I will briefly review the anatomy of the hippocampal formation as this is a necessary foundation for the entire review. I will then describe early studies that highlighted the necessity of proper hippocampal function for memory formation, although this section will be brief because this area has been covered extensively in the literature already and is given adequate treatment in a number of standard textbooks in the area (Kandel et al. 1995; Squire and Kandel 1999; Squire et al. 2002). I will then proceed to providing a few examples for each of the three additional areas of cognition in which the hippocampus is involved, which, as described above, are termed space, time, and relationships.

Anatomy of the hippocampal formation

As shown in Fig. 1, the hippocampus is both downstream and upstream of essentially all the cortical association regions of the CNS (Squire and Zola-Morgan 1991). This fact in itself suggests that the hippocampus is part of a multi-modal sensory integration system in the central nervous system. I will bolster this anatomical argument with a variety of functional data in the last three sections of this review.

Sensory information from the various cortical areas is funneled down to the hippocampus via the perirhinal and entorhinal cortices; these are the cortical areas in the immediate anatomical vicinity of the hippocampus near the rhinal fissure in the temporal lobe. The outputs of the

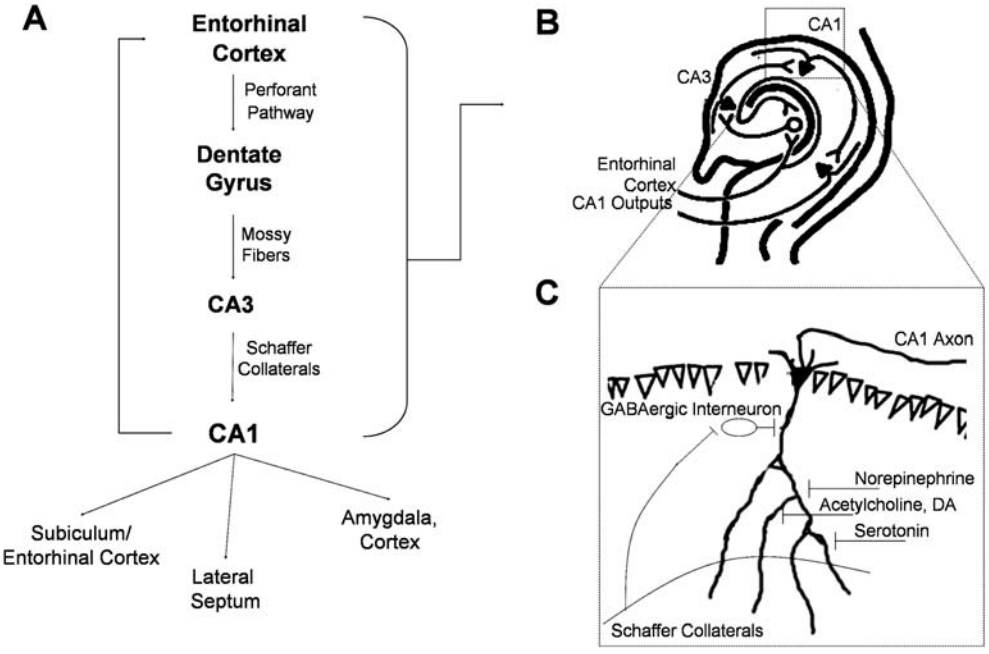

Fig. 2 Hippocampal intrinsic circuit and output pathways. Schematic and illustration of the principal pathway through the hippocampus. On the *left* is a schematic of the structures through which the sensory signal travels within the hippocampal formation. *Top right* is a more realistic drawing of these structures (Squire and Zola-Morgan 1991). *Bottom right* shows the signaling occurring in area CA1 of the hippocampus, focusing on the cellular connections

perirhinal and entorhinal cortices then project to the dentate gyrus and the hippocampus proper (these two are referred to jointly as the hippocampal formation).

The hippocampus proper is also known as Cornu Ammonis (Ammon's horn) because of its shape. The Cornu Ammonis terminology leads to four anatomical subdivisions of the hippocampus: areas CA1, CA2, CA3, and CA4. Areas CA1 and CA3 are the largest and most easily identified. The principal neurons in the CA regions are called pyramidal neurons because of their shape—they comprise about 90% of all the neurons in the CA regions of the hippocampal formation. The output neurons of the hippocampus are the CA1 pyramidal neurons—their axons are glutamatergic, and it is via these axons that information leaves the hippocampus proper. The axons of CA1 neurons project predominantly to the ipsilateral and contralateral entorhinal cortices, but additional direct outputs of CA1 neurons project to the contralateral hippocampus via the fornix (Fig. 2). Secondary efferents of CA1 pyramidal neurons via the subicular neurons also project to subcortical regions including the ventral striatum and mammillary bodies.

Thus, we can see that information goes out of the hippocampus and ultimately back up into the cortex in its principal pathway, back-tracking its way once again through the entorhinal and perirhinal cortices. I emphasize this because it is important to remember that these cortical areas immediately adjacent to the hippocampal formation are functionally an extension of the hippocampus (and vice-versa). This is worth noting because although I will frequently use the term "hippocampus dependent," any phenomenon thus described might equally well be described as entorhinal cortex dependent or perirhinal cortex dependent. The hippocampal formation and its adjacent cortical regions function in tandem in both memory formation and cognitive processing (Lavenex and Amaral 2000).

Before leaving the topic of cortical inputs into the hippocampus, it is worth emphasizing specifically that the prefrontal cortex and hippocampus are functionally interconnected (Burwell and Amaral 1998). On the hippocampal input side, this connection is from the prefrontal cortex to the entorhinal, perirhinal, and parahippocampal cortices and thence on to the hippocampus proper. The existence of these connections has in part led to the general view of the prefrontal cortex as part of a sensory-motor-limbic integration system. Consistent with this view are the reciprocal connections from the hippocampus back to the prefrontal cortex. These fall into two broad categories. First are the projections from the CA1 pyramidal neurons and subicular neurons to the entorhinal and perirhinal cortices, which then provide efferent innervation back to the prefrontal cortex. A second, more direct route is a projection from CA1 pyramidal neurons onto prefrontal cortex neurons themselves (Swanson 1981).

This integration of hippocampus and prefrontal cortex is important as one considers a potential role for the hippocampus in cognition in general and schizophrenia in particular, given the widely recognized involvement of dysfunction of the prefrontal cortical areas in schizophrenia. As the hippocampus is one unit that interacts with the prefrontal cortex, dysfunction in each area might precipitate or exacerbate dysfunction in the other. This consideration is likely relevant for all the various types of information processing that are discussed in this review and, in my opinion, perhaps the hippocampus hasn't received the attention that it deserves in this context.

Finally, I note that, as is shown in Fig. 2, the hippocampus receives a wide variety of extrinsic inputs of various neuromodulatory neurotransmitters. These

include projection fibers that are serotonergic, dopaminergic, cholinergic, and noradrenergic. There also are intrinsic interneurons in the hippocampus that are GABAergic, and numerous peptide neuromodulators including reelin, BDNF, NGF, etc., which all are present in the hippocampus. The intrinsic connections between pyramidal neurons in the hippocampus are glutamatergic. I list these neurotransmitter systems to make the point that essentially all the wide variety of neuromodulators hypothesized to be involved in schizophrenia are present and important for hippocampal function.

Although there is not room to go into the function of these various transmitters and neuromodulators in detail in this short review, it is worth noting that, in general, all these agents help function to optimize hippocampal function. For example GABA, acetylcholine, norepinephrine, and serotonin all participate in synchronizing hippocampal neuron firing patterns by various mechanisms, effects which are associated with both memory formation and cognitive processing. BDNF and reelin, while typically thought of as trophic factors, also have acute effects on synaptic function in the adult hippocampus. Both these large peptides function as neuromodulators controlling the likelihood of triggering long-lasting changes in hippocampal synaptic function. Of course the function of glutamate receptors, including the NMDA receptors integral to long-term synaptic plasticity in the hippocampus, is necessary for proper function of the hippocampus and attendant cognitive processing.

In fact, recent studies from my laboratory and a variety of others indicate that hippocampal pyramidal neurons in area CA1 are on a second-to-second basis integrating all of these different neurotransmitter inputs (Sweatt 2001, 2003). This signal integration is important in regulating synaptic function and in controlling the likelihood of triggering lasting changes in synaptic strength. Thus, all of these signaling mechanisms converge on CA1 pyramidal neurons and their synapses. In particular, these types of modulatory inputs regulate NMDA receptor function in the hippocampus, and control the likelihood of triggering long-term potentiation.

Thus, a multitude of schizophrenia-related drug targets are quite likely functionally relevant for the optimal operation of the hippocampus. This is worth keeping in mind both in terms of therapeutic effects and undesirable side effects of novel cognitive treatments in schizophrenia.

As described above, the general roles of the hippocampus and associated cortices appear to be at least two-fold. One role is to process information of a wide variety of sorts, which we will discuss in the last three sections of this review. The second general function is to download information into the cortex for storage as long-term memory, which we will discuss in the next section.

The hippocampus in memory consolidation

Very early in the study of memory mechanisms, it became clear that memories are labile. Any number of different types of insults occurring immediately after a training period can cause the loss of a memory that would normally be stored in a lasting fashion. This is illustrated nicely in experiments where protein synthesis inhibitors are infused into an animal's CNS immediately after training, which results in a loss of effective memory storage (McGaugh 2000). The period of susceptibility to disruption typically lasts several hours post-training, and this fundamental observation led to the idea that memories are "consolidated" or rendered long-lasting over the period of time immediately following training.

There is a wide variety of evidence, too extensive to reiterate here in detail, that the hippocampus is involved in and required for long-term memory consolidation. A brief overview of the types of experiments indicating a role for the hippocampus includes: lesioning studies, post-training drug-infusion studies, studies of molecular changes in the hippocampus after training, in vivo cellular recordings, and selective genetic engineering of the hippocampus. Exactly how the hippocampus triggers memory consolidation is a very active area of research at present, and the cellular and molecular basis of memory consolidation is one of the most intriguing areas of contemporary neuroscience research. However, studies of this sort are still at a relatively early stage and no unifying model is currently available concerning the precise mechanisms involved. Nevertheless, the involvement of the hippocampus in memory consolidation has at least been firmly established experimentally using the wide variety of approaches listed above (Martin and Morris 2002).

I will highlight only one seminal finding from human studies to illustrate the point of the necessity of the hippocampus for human memory consolidation. This study involved the patient H.M. (Milner et al. 1998). Figure 3 shows a magnetic resonance image (MRI) of this patient's CNS, illustrating his hippocampal lesions compared with that of a control subject. H.M. underwent experimental surgery, a bilateral hippocampectomy, to help control his intractable epilepsy. This had an unfortunate and unintended consequence, causing essentially total anterograde amnesia. H.M. has from the point of his surgery been unable to effectively form long-term memories.

Characterization of the memory deficits in H.M. provided a turning point in the history of cognitive neuroscience. It became clear that H.M. had selective deficits in certain types of memory, for example. Some memory systems were still intact, and thus hippocampus independent. Studies of H.M. and patients like him with hippocampal lesions led to a new classification system for different types of memory in the human (Fig. 4). Declarative memories, facts and personal experiences, are dependent on the hippocampus and medial temporal lobe for their formation. Many other types of memories, including motor learning and many types of associative conditioning, are hippocampus independent.

Participation in declarative memory consolidation is certainly the prototypical and dogmatic function of the hippocampus. In the present context, it certainly bears

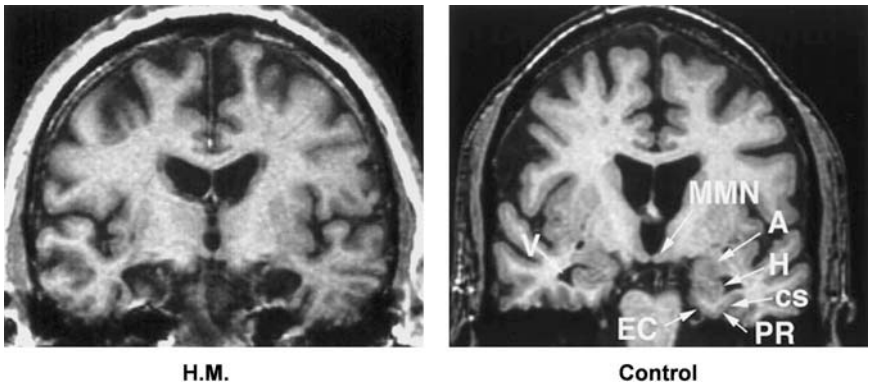

Fig. 3 Magnetic resonance image of patient H.M.'s brain lesions. *Left* Scan showing the removal of medial temporal lobe structures in H.M. The lesion included all of the entorhinal cortex, most of the perirhinal cortex and amygdala, and about half of the hippocampus. *Right* Scan of control subject. *A* amygdala, *cs* collateral sulcus, *EC* entorhinal cortex, *H* hippocampus, *MMN* medial mammillary nucleus, *PR* perirhinal cortex. Reproduced from Corkin et al. (1997)

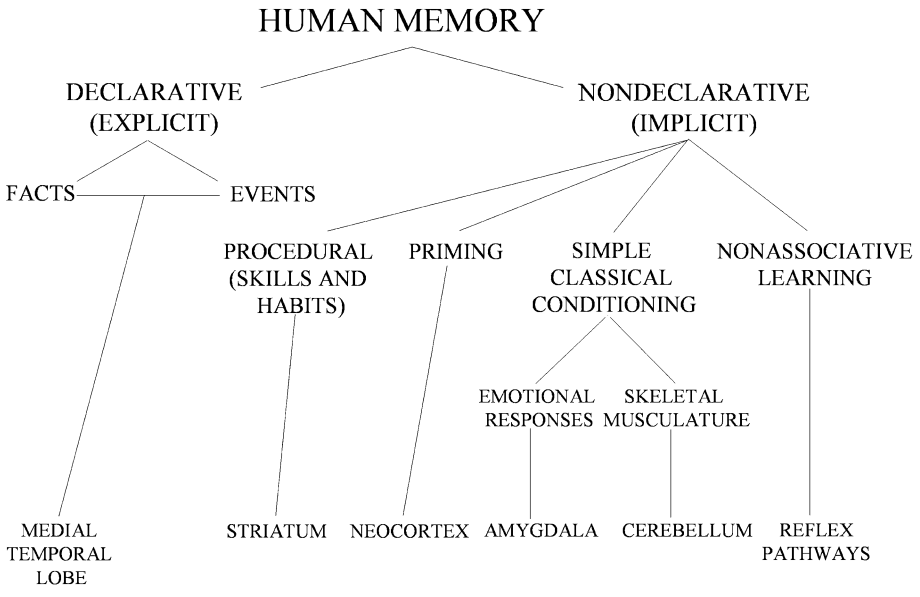

Fig. 4 Subdivisions of human memory and associated brain regions. Human memory is typically divided into declarative and non-declarative types, also known as explicit and implicit memory, respectively. Chart adapted from Milner et al. (1998). This type of chart, subdividing memory into several, separately identified components distills the modern concept of multiple memory systems. It is now clear that different anatomical structures in the brain are involved in different types of memory formation. Moreover, the different systems can operate as parallel processors, operating independently. This allows multi-tasking, with conscious and unconscious memory systems operating simultaneously and increasing the overall "memory throughput" of the central nervous system. I highly recommend reading *From Conditioning to Conscious Recollection* by Eichenbaum and Cohen (2001) for a more thorough treatment of the multiple memory systems concept

emphasizing that the hippocampus is integral to memory formation, and this role is certainly germane to considering a role of hippocampal dysfunction in the ontogeny of cognitive deficits in schizophrenia. The new thinking in this area that will be the focus of the rest of this review shouldn't diminish one's appreciation of this fact.

However, as I mentioned, there's accumulating evidence that the hippocampus is involved in on-going cognitive processing as well as memory consolidation. It is not necessarily the case that these functions are independent of memory consolidation, in that they may be a precursor to the formation of memories. But certainly in thinking about hippocampal derangements in schizophrenia, careful consideration of the general role of the hippocampus in perception of the environment and ongoing cognitive processing is warranted.

As I mentioned above, in describing what the hippocampus is doing on a minute-to-minute basis in cognition, I use the mnemonic device of the hippocampus being involved in space, time and relationships. In the following section I'll explain what I mean by that with a few specific examples for each category. In all cases, the examples draw from in vivo recordings of hippocampal CA1 pyramidal neuron firing, obtained while an animal is exploring and learning about its environment. I will draw my examples from the pioneering work of O'Keefe and

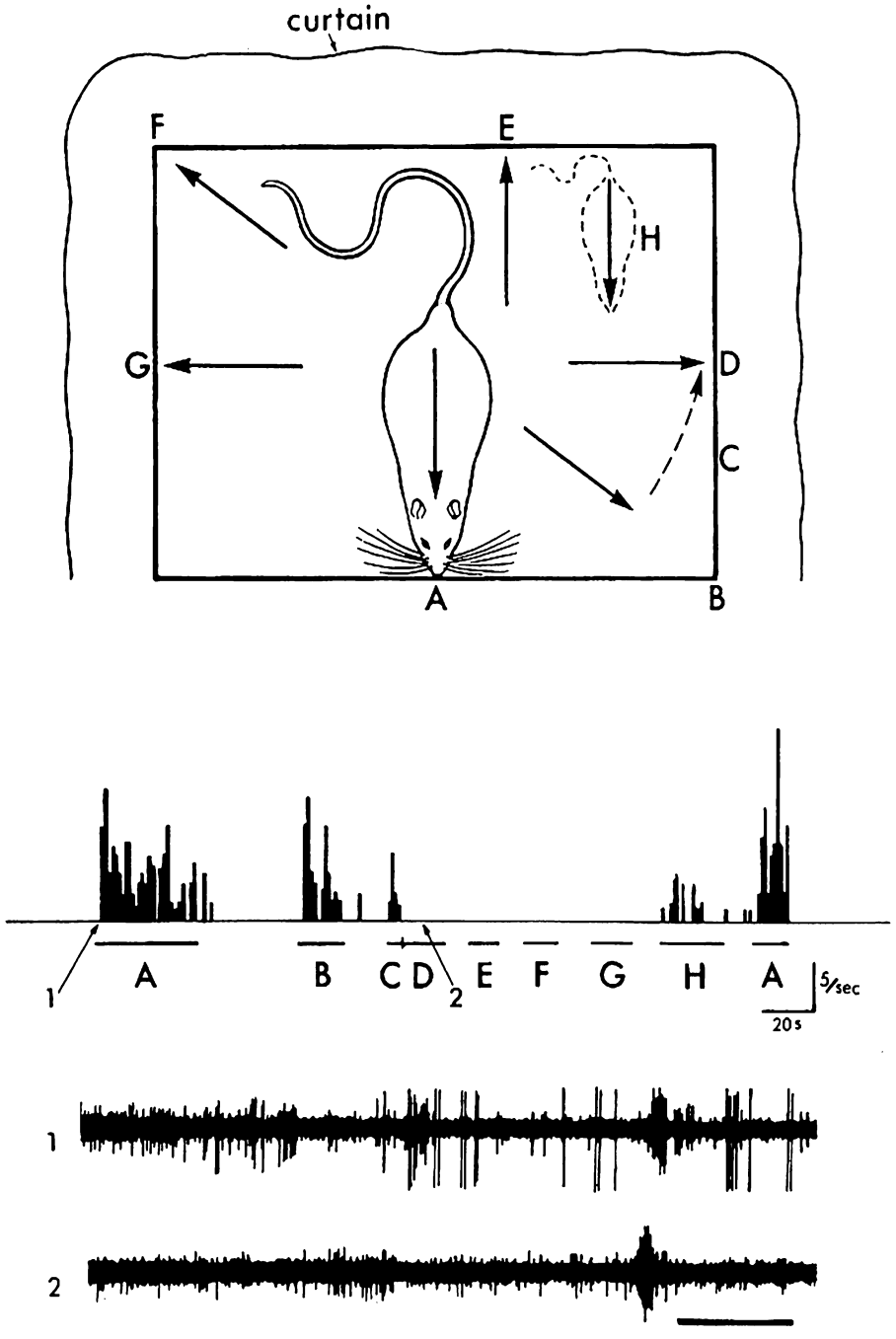

Fig. 5 Place-cell firing patterns. This figure is from an early place-cell firing report from O'Keefe and Dostrovsky (1971). Place cells only fired in position A as shown in *top diagram*. *Below*, histogram of firing at each location in the diagram and raw firing patterns during periods marked *1* and *2* in the histogram. Figure reproduced from O'Keefe and Dostrovsky (1971)

Dostrofsky (1971), and from beautiful work done recently in the laboratories of John Disterhoft and Howard Eichenbaum.

The hippocampus in spatial cognition

The first example that we will discuss is spatial information processing. Pioneering work in this area utilized in vivo recordings from the hippocampus of behaving rats. This general approach seeks to gain insights into hippocampal function by putting an electrode in the hippocampus to find out what's happening in there when the animal is exploring its environment and processing sensory information on an active basis. For this example, as well as the remainder of the review, I'm going to discuss recordings of action potential firing patterns, recorded extracellularly from single area CA1 pyramidal neurons. It is worth keeping in mind that these firing patterns are responses to the complex synaptic inputs that cause membrane depolarization and modulation of membrane excitability in these neurons (Fig. 2).

Early studies in this area showed a striking effect. If you put a recording electrode in the hippocampus of a rat, put the animal in an open field, and allow it to walk around, then you see that when the animal is in a particular place

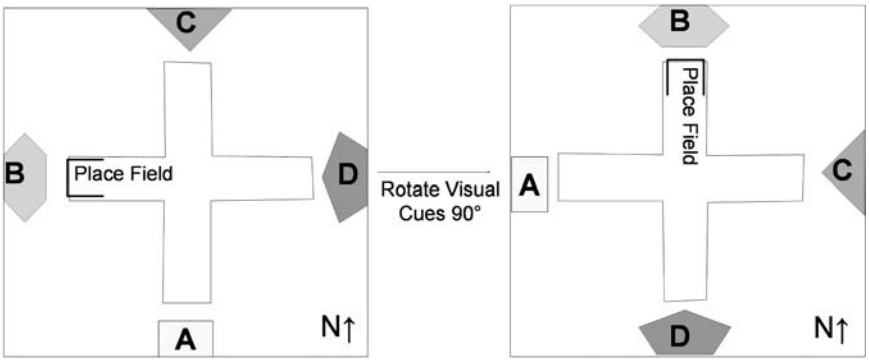

Fig. 6 Place cells follow rotation of visual cues. Diagram of 4-arm radial maze set-up. In this test the maze remains stationary while the visual cues on the walls are rotated 90° clockwise. When the animal is placed in the first set-up the place field is in the arm closest to the cue marked *B* (the western arm before the rotation). When the cues are rotated, the place field is again in the arm closest to the cue marked *B* (the northern arm after the rotation). This indicates that the place field is located by the animal's relationship to the distal visual cues, not the animal's absolute location in the room

with a particular orientation, there's a high firing rate for particular cells. When the animal is in other locations in the open area, there's low or no firing of the same cells. Please see Fig. 5 for an example of this type of position-specific cell firing, which is taken from one of the earliest studies describing this property of hippocampal pyramidal neurons (O'Keefe and Dostrovsky 1971). Findings like this generated the idea of hippocampal neurons as "place" cells. As an extension of this idea, the particular area of the open field for which a given pyramidal neuron fires is referred to as its "place field". The take-home message from these early studies is that the rate of firing of single pyramidal neurons in area CA1 seems to be encoding a specific spatial location, based on cues from the environment.

Visual cues in the environment are important in determining place-cell firing. This is illustrated by the example diagrammed in Fig. 6. If you put the animal in a plus-shaped maze, place-field firing patterns will form as expected. For example, a given pyramidal neuron will fire selectively in a specific area of the maze: in the example in Fig. 6 the neuron fires specifically only when the animal is in the distal end of the left-hand arm. If you rotate the visual cues 90°, but leave the maze in exactly the same absolute position, the firing of that neuron follows these visual cues in three-dimensional space. The cell is not firing when the animal is in the west arm of the maze; it is firing when the animal perceives itself to be in a particular position relative to the four visual cues available to it (or perhaps the cell is telling the animal to perceive itself to be in a particular position; we don't know whether the place cell is upstream or downstream of the perception). This experiment illustrates that hippocampal pyramidal neurons fire specifically when an animal's environmental cues tell it that it is in a particular spatial location. The results also eliminate the alternative explanation that the hippocampus is simply a part of environment-independent navigation system such as that of a homing pigeon that detects the earth's magnetic field in an absolute sense. Thus, the cell clearly is participating in forming an abstract construct—the spatial relationship of the animal to its environment.

However, you might ask yourself the following question: what if the animal has both distal cues on the wall and local cues within the maze and you rotate the distal cues 90° in one direction and the local cues 90° in the opposite direction? What happens to the place-cell firing pattern? The answer is that individual cells can do a lot of different things, as is illustrated in Fig. 7. Some cells track distal cues exclusively. Some cells track local cues exclusively. Some cells—as illustrated by "Cell 4" in Fig. 7—track both. In the last example, if the cell originally fires in a specific arm of the maze, after the double rotation of the distal and local cues, it fires both in response to the new location in space encoded by the distal cues and in response to the new location of the local cues (Tanila et al. 1997a). This observation indicates that hippocampal pyramidal neuron function is even more complex than the cells operating as "place cells". Some pyramidal neurons thus also appear to be "local cue cells", or even "local cue plus distal cue cells".

These observations begin to get to the important issue that hippocampal pyramidal neurons are in fact forming a synthesis of environmental cues that are used for cognitive processing by the animal. It has become very clear over the last 5 years or so that CA1 pyramidal neurons are much more than just place cells. This is also illustrated nicely in Fig. 8, which shows the place cell firing pattern of a hippocampal neuron when the animal is in an open field (Hetherington and Shapiro 1997). The animal has three cue cards visible to it when it is in the apparatus. If one of the cue cards is removed, there is very little effect on the place cell firing pattern (panel B). However, when a different card is removed, the peak firing rate decreases significantly (panel C). The place-field firing is maintained, but only at a reduced rate! So yet again this observation suggests that the animal is forming a synthesis of a multiple visual inputs, and it's reflected in the firing pattern of the CA1 pyramidal neurons.

These are just a few examples to illustrate the point that CA1 pyramidal neurons in the hippocampus are involved in cognitive processing of space. They participate in forming a synthetic construct of environmental cues,

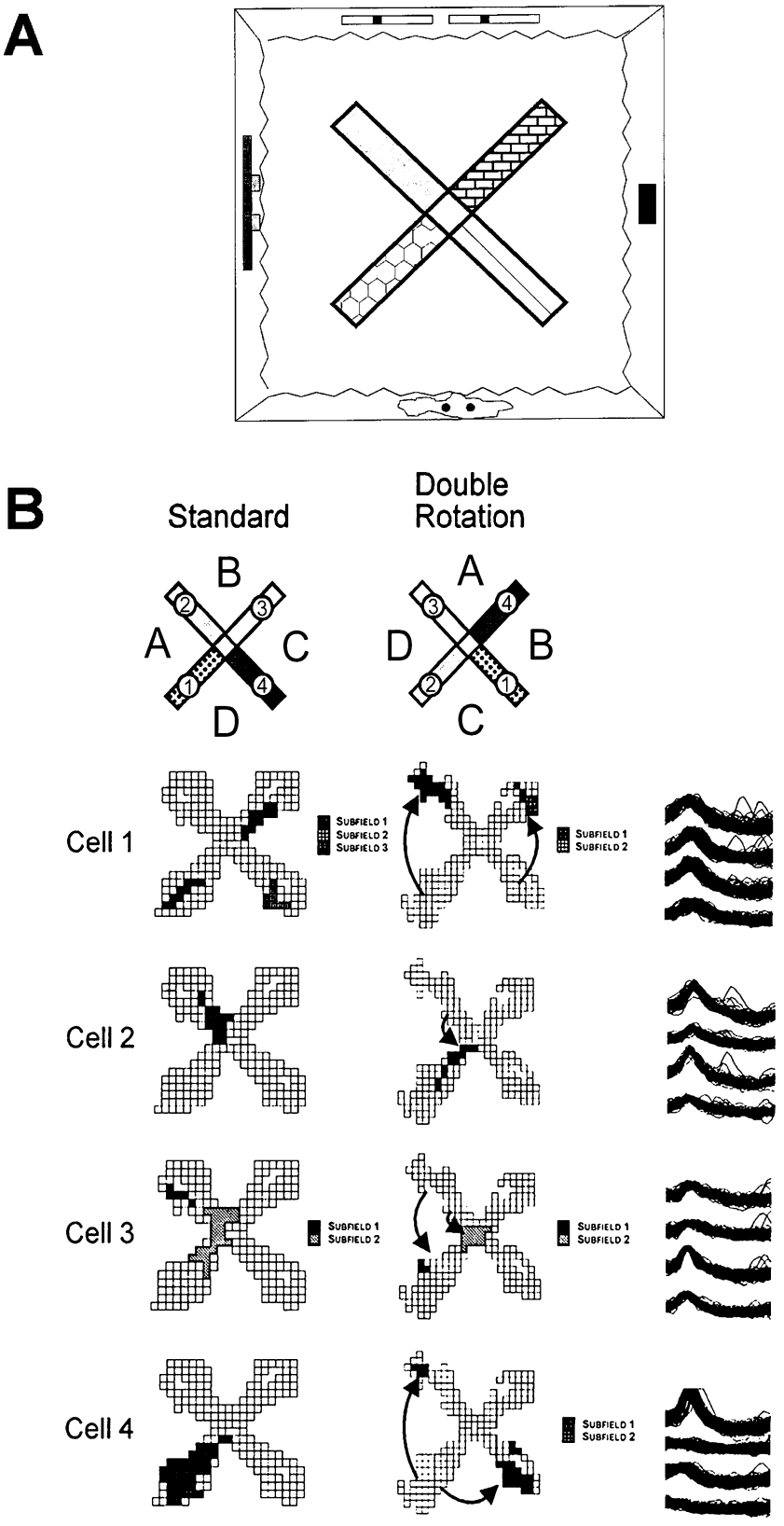

Fig. 7 4-Arm radial maze with local and distal cues. **A** Diagram of the 4-arm radial maze set-up used in the experiments such as those performed by Tanila et al. 1997a, 1997b (see text). This maze is used to assess effects of manipulation of local and distal cues. Local cues are coverings of the arms that give a set of visual, tactile and olfactory cues distinct form the other arms. The distal cues are objects on each wall surrounding the maze. Reproduced from Tanila et al. (1997b). **B** Double-rotation 4-arm maze experiment. In this experiment, the four local cues were rotated 90° to the left as the distal cues were rotated 90° to the right. The responses of four simultaneously recorded cells (cells 1–4) are shown here before and after the double rotation of the cues. Some cells follow local cues, some follow distal cues, and some follow both cues. Data and figure reproduced from Tanila et al. (1997a). Copyright John Wiley and Sons, Inc

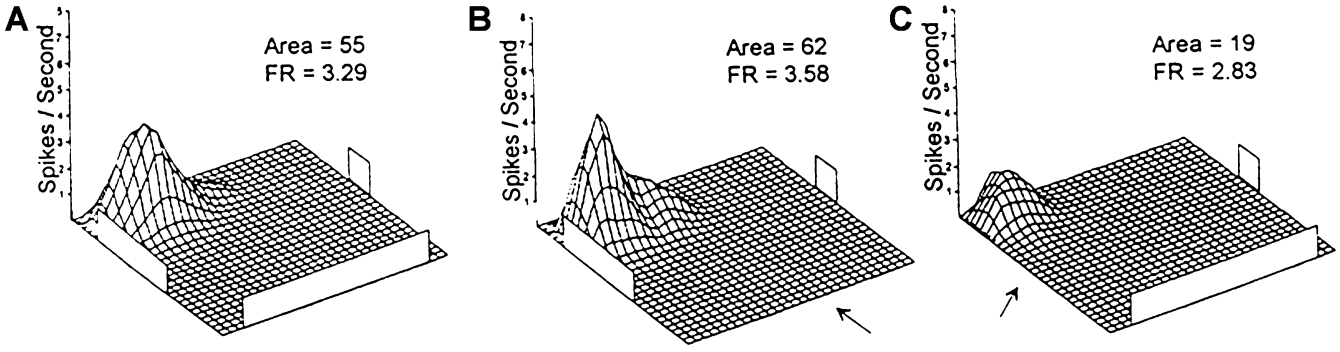

Fig. 8 Place-cell firing pattern during open-field test. **A** Firing pattern of a hippocampal neuron when all three visual cues are present. **B** Place-cell firing patterns when one cue is removed, and **C** when a different cue is removed (*arrow* indicates which cue is removed). See text for discussion (Hetherington and Shapiro 1997)

Fig. 9 Eye-blink conditioning in rabbits. Animals are trained in a Pavlovian conditioning paradigm to learn that a tone predicts a puff of air to the eye surface. Over time the animals learn to blink in response to the tone alone. See text for additional details

presumably to help provide a unified cognitive construct of the animal's relationship to the context in which it finds itself. In the next section, we will transition from the role of the hippocampus in spatial cognition to the issue of the hippocampus being involved in information related to time.

The hippocampus in temporal information processing and sequencing

I will present three brief illustrations of what I mean by the hippocampus being involved in processing "time." I don't mean time in the sense that you're probably thinking about it, that is the absolute perception of time (although this cannot be ruled out). What I am referring to is a role for the hippocampus in time-dependent learning and in perceiving the temporal ordering of environmental signals (Clark and Squire 1998).

I will use trace eye-blink conditioning as the first example. In the eye-blink conditioning paradigm, the animal learns to associate an auditory cue with a mild air puff delivered to the surface of its eye (Fig. 9). In eye-blink conditioning, the animal learns to blink a set period of time after the auditory cue, in order to protect its eye from the air puff. Because the auditory cue is separated from the puff of air to the cornea by an intervening period, this is specifically referred to as a "trace" conditioning paradigm in the animal behavior literature (Fig. 10A). Delay conditioning has no time lag between the auditory cue and the air puff. Both trace and delay conditioning are forms of classical, Pavlovian conditioning. However, the introduction of the intervening time period between auditory cue (conditioned stimulus, CS) and air puff (unconditioned stimulus, US) selectively recruits the involvement of the hippocampus in both humans and rodents.

In seminal studies of hippocampal responses during trace-associative eye-blink conditioning, John Disterhoft's lab investigated hippocampal neuron firing patterns during the period of environmental stimulation and during the time period between the auditory cue and the air puff (McEchron and Disterhoft 1997; Power et al. 1997). As is nicely illustrated in Fig. 10B, a subset of hippocampal pyramidal neurons fire repeatedly over the period of time between the CS and US. Pyramidal neurons exhibiting this pattern of firing appear to be serving in a "time-keeping" role. They may be encoding the time delay after which the animal should expect the air-puff, or they may be serving as a cellular stopwatch to help encode the CS–US interval. Regardless, these data indicate that the hippocampus is involved in temporal cognition in trace-associative conditioning (McEchron et al. 2003).

It is worth noting in passing that this pattern of neuronal firing is reminiscent of firing patterns seen in prefrontal cortex neurons as well. I point this out given the substantial evidence implicating the prefrontal cortex as an area potentially involved in cognitive derangements in schizophrenia. The similarities in firing patterns between the hippocampus and prefrontal cortex might suggest a functional connection between the two areas related to "time-keeping" and, by extension, provide an additional line of reasoning for suspecting hippocampal dysfunction as a contributing factor in cognitive dysfunction in schizophrenia.

Before proceeding to the last area of discussion, I would like to briefly mention two recent studies from Howard Eichenbaum's laboratory which also have great bearing on potential roles for the hippocampus in temporal cognition. In these studies, Agster et al. (2002) and Fortin et al.

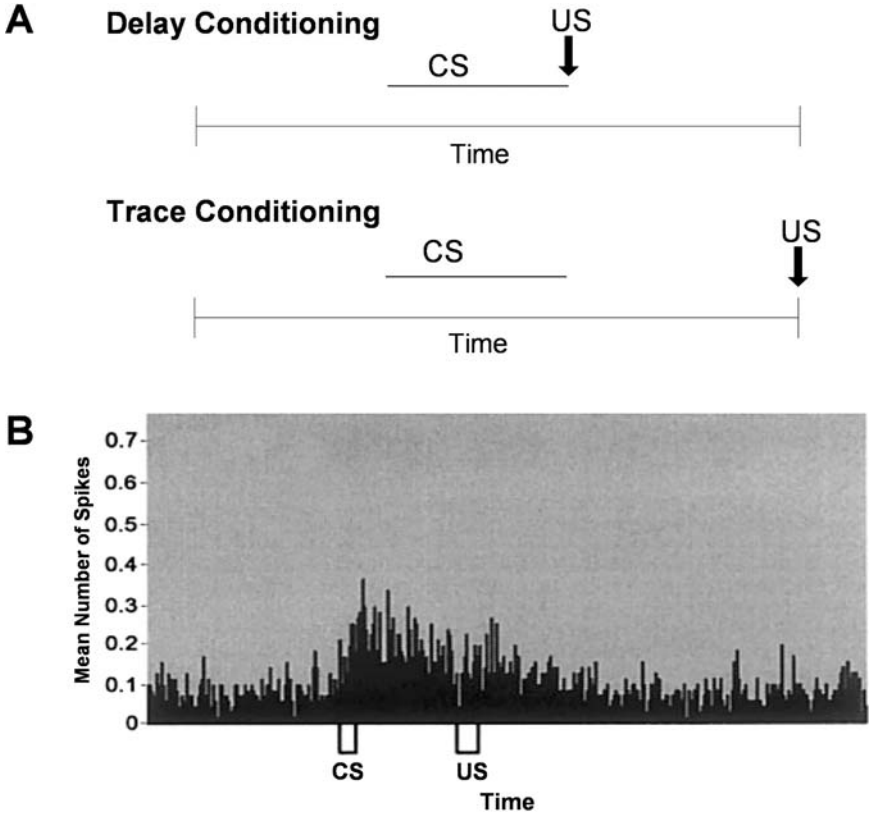

Fig. 10 Delay and trace conditioning. Associative conditioning falls into two broad categories—delay conditioning and trace conditioning. In trace conditioning an intervening time interval is introduced between the termination of the conditioned stimulus (CS) and the onset of the unconditioned stimulus (US). Trace conditioning involves the hippocampus. **B** Increased hippocampal neuron firing during trace eyeblink conditioning. Average peri-event histograms (10-ms bins) for pyramidal cell response profile recorded from rabbits during trace conditioning. Action potentials (spikes) from each cell were summed across a single training session, then averaged across cells. The duration of the histogram is 3750 ms, and the duration of the baseline period prior to CS onset is 1000 ms. Of all tested pyramidal cells, 7.4% displayed this type of response profile. Data and figure from McEchron et al. (2001). It is worth noting that many neocortical neurons exhibit this same type of firing pattern, that is, a residual increase in firing after the presentation of an environmental stimulus. This has been most extensively documented in neurons in the visual system and prefrontal cortex. This is important to keep in mind because clearly the hippocampus is not the only area of the brain encoding temporal information

(2002) implicated the hippocampus in the ability of animals to remember sequences of odor presentation. In the first study, Fortin et al. studied the capacity of rats to remember sequences of odors, assessed behaviorally with a reward paradigm. They found that hippocampal lesions produced a severe and selective impairment in the capacity of rats to remember the sequence of a series of odors over time, despite an intact capacity to recognize the same odors when they had recently occurred. These findings support the idea that hippocampal function mediates associations between sequential events that constitutes an episodic memory.

In a complementary study, Agster et al. (2002) trained rats to distinguish two overlapping sequences of odor choices. The rat's capacity to differentiate between the two different sequences of the same odors was determined using a choice task as a read out. When the odor sequences were presented, spaced apart from each other, animals with hippocampal lesions could perform the task normally. However, when the sequences were presented in rapid alternation closely in time, damage to the hippocampus produced a severe deficit in the animals distinguishing the different sequences. In addition, when a long delay was imposed before the choice task, hippocampally lesioned animals exhibited a deficit. Both of these studies from Eichenbaum's group support the idea that the hippocampus is involved in representing sequences of events, particularly when interference between the sequences is high or when animals must remember across a substantial time delay.

Again, these observations are indicative of a role for the hippocampus in time-based cognitive processing. Moreover, these observations are reminiscent of certain temporal ordering deficits manifested by schizophrenic patients, and are consistent with recent findings by Schendan et al. (2003) suggesting temporal lobe involvement in sequence learning in humans.

The hippocampus in multimodal sensory integration

In this last section, I will discuss what I mean by the hippocampus being involved in "relationships." The gist of it is that the hippocampus is involved in forming multi-

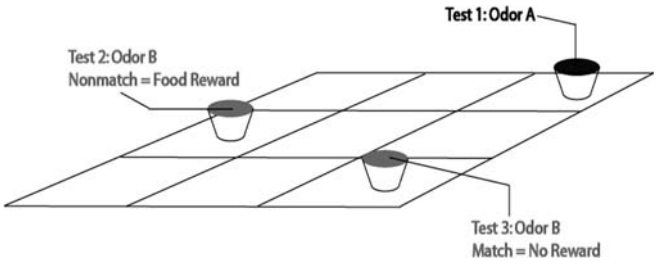

Fig. 11 Continuous odor-guided non-matching to sample task. This diagram outlines an experiment used to assess the ability of the animal to distinguish between a matching or non-matching stimulus. The animal must determine whether the second smell that they experience is the same or different than the first, if the third is the same or different than the second and so on. In this example, test one has odor A; test two has odor B, a non-match. Test three also has odor B so the third is a match to the second. Only non-matches contain a food reward. The different odor cups are presented sequentially in different, random locations in the test field

modal representations of complex environmental cues. I will illustrate this by describing a beautiful experiment that was performed by Emma Wood and Paul Dudchenko in Howard Eichenbaum's laboratory (Wood et al. 1999). In this series of studies, they trained an animal in an open platform to do a delayed non-matching-to-sample task. The paradigm is based on olfactory cues in small cups placed at any one of nine different locations in an open matrix. One cup at a time was placed in the open field, with different odors being presented in a random fashion (Fig. 11). The odor cups were also presented in random positions in the open field, that is, randomly at any one of the nine possible positions in the matrix. In this task the animal has to learn that if the odor in any cup does not match the odor that was present in the cup immediately before it, then it gets a reward. If the two odors in succession are a match, then it gets no reward.

The beauty of this experiment is that Wood, Dudchenko, and Eichenbaum recorded from the hippocampus while the animal was performing the task (Wood et al. 1999). Therefore they were able to record hippocampal neuron responses while the animal was in an open field (you can start thinking about place cells), but they also could record hippocampal responses while the animal was doing the delayed non-match-to-sample cognitive task at the same time.

What types of hippocampal cellular firing patterns did they observe? An amazing diversity! Wood et al. observed basic odor-selective cells (Fig. 12) that respond to a particular odor. Of course, they observed position-depen-

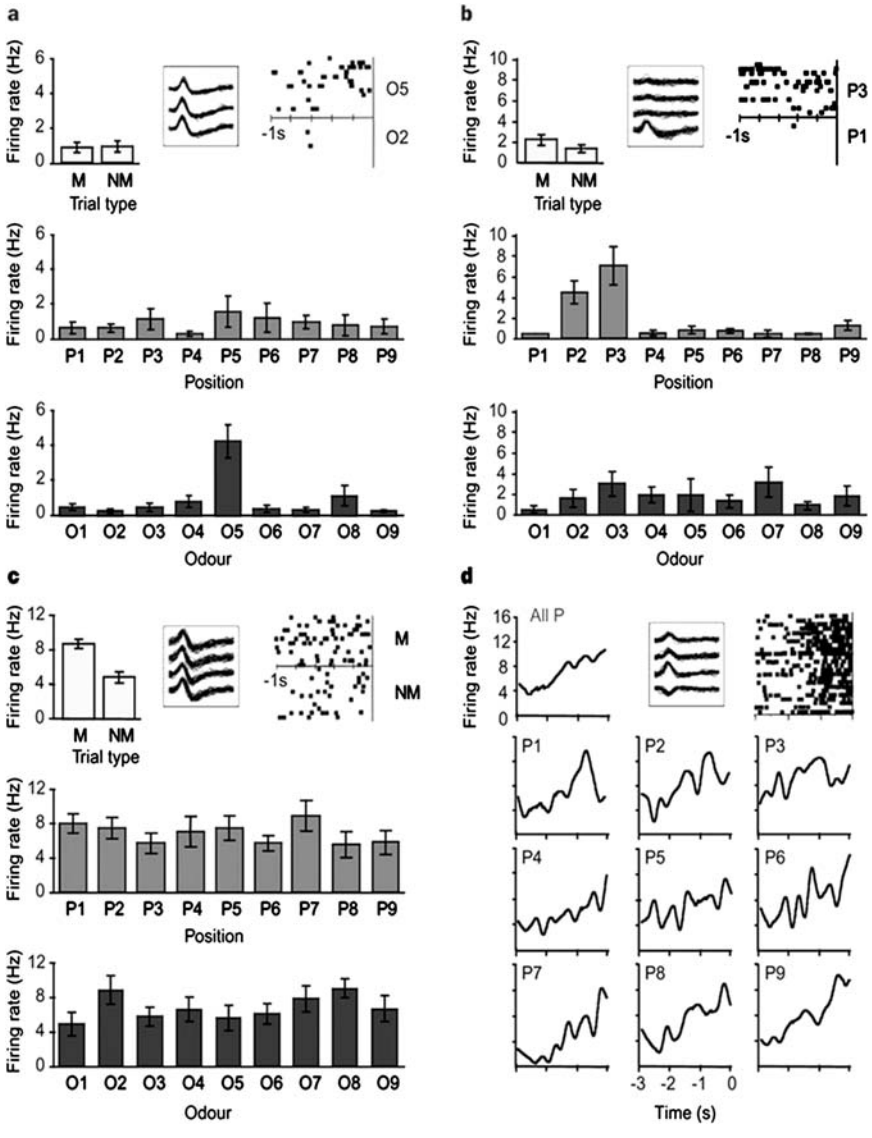

Fig. 12 Task-related firing patterns of hippocampal pyramidal neurons. Panels a–c in this figure show the firing rate in a 1-s analysis period for each trial type (*M* match; *NM* non-match), cup location (P1-P9) and odor (O1-O9) for three different types of cells: **a** an odor cell [odor, $F_{8,74}$=8.59, P<0.0001; trial type, $F_{1,74}$=0.04, not significant (NS); cup location $F_{(8,74)}$=1.03,NS; odor x trial type, $F_{(8,74)}$=1.74, NS]; **b** a location cell [cup location, $F_{8,74}$=8.60, P<0.0001; odor, $F_{8,74}$=0.84, NS; trial type $F_{1,74}$=2.76, NS; odor × trial type, $F_{8,74}$=1.14, NS; cup location × trial type, $F_{8,74}$=1.58, NS]; **c** a match cell [trial type, $F_{1,74}$=22.95, P<0.0001; odor, $F_{8,74}$=1.42, NS; location, $F_{8,74}$=1.17, NS; odor × trial type, $F_{8,74}$=0.68, NS; location × trial type, $F_{8,74}$=1.20, NS]. **d** Firing rates (200-ms bins) for a 3-s period when the rat approached each cup position (P1–P9), and averaged across all positions (all *P*) for an approach cell (trial period, $t_{1,107}$=10.77, P<0.001; trial type, $F_{1,74}$=0.06, NS; odor $F_{8,74}$=0.47, NS; location $F_{8,74}$=1.42, NS; odor × trial type, $F_{8,74}$=0.96, NS; location × trial type, $F_{8,74}$=1.00, NS). Each *panel* also shows the waveform of the cell recorded on each tetrode channel and a raster display of firing patterns time-locked to the end of the odor sample period. Data, figure and figure legend reproduced from Wood et al. (1999)

dent cells that are prototypical place cells. However, they also observed cells that fired selectively on an odor match or a non-match. They observed cells that fired selectively when the animal was approaching the odor-containing cup. The upshot of all this is that hippocampal pyramidal neurons are not just place cells; they're also "odor" cells and "contingency" cells and "object" cells.

An additional implication of this finding, especially when considered alongside the other examples above concerning hippocampal neuron firing patterns, is that hippocampal pyramidal neurons are participating in forming a multi-modal representation of numerous cues in the environment, and their relationship to each other. A single pyramidal neuron may fire only upon presentation of several environmental cues simultaneously. Another pyramidal neuron (or the same one at a different time) may fire only when it is immediately preceded by a different cue in a predictable fashion. Other cells fire only in response to a particular cue when the animal knows that that cue will lead to a reward. These types of firing patterns suggest that the pyramidal neuron is encoding the relationship of one signal in the environment to another cue in the environment, forming a unique synthesis.

In conclusion then, as opposed to thinking about the hippocampus as simply being involved in memory consolidation or even in spatial learning or spatial information processing, it's useful to begin thinking about the hippocampus as contributing to cognitive processing of the relationships of environmental cues to each other. These relationships may be spatial, temporal, or based on contingencies.

Summary

To reiterate: the hippocampus is involved in cognitive processing of space, time and relationships of environmental cues to each other. This is in addition to its classical role in memory consolidation. These functions are quite reminiscent of specific aspects of cognitive dysfunction in schizophrenic patients, and these findings support the hypothesis of hippocampal dysfunction as being involved in cognitive disruption in schizophrenia. By extension, this suggests to me and many others—as has been discussed in numerous articles in this special issue of *Psychopharmacology*—that cognition-enhancing drugs have a rightful place in the armamentarium of drugs useful for treating schizophrenia. Hopefully, continued advancements in understanding the cellular and molecular basis of cognition will shed new light on promising avenues for new drug treatment in this context.

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