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Toward an Integrative Perspective on Hippocampal Function: From the Rapid Encoding of Experience to Adaptive Behavior

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SYNOPSIS

The mammalian hippocampus has been associated with learning and memory, as well as with many other behavioral processes. In this article, these different perspectives are brought together, and it is pointed out that integration of diverse functional domains may be a key feature enabling the hippocampus to support not only the encoding and retrieval of certain memory representations, but also their translation into adaptive behavior. The hippocampus appears to combine: (i) sensory afferents and synaptic mechanisms underlying certain types of rapid learning; and (ii) links to motivational, emotional, executive, and sensorimotor functions. Recent experiments are highlighted, indicating that the induction of hippocampal synaptic plasticity is required to encode rapidly aspects of experience, such as places, into memory representations; subsequent retrieval of these representations requires transmission through the previously modified hippocampal synapses, but no further plasticity. In contrast, slow incremental place learning may not absolutely require hippocampal contributions. The neocortical sensory inputs, especially visuo-spatial information, necessary for hippocampus-dependent rapid learning, are preferentially associated with the septal to intermediate hippocampus. In contrast, connectivity with the prefrontal cortex and subcortical sites, which link the hippocampus to motivational, emotional, executive, and sensorimotor functions, is primarily associated with the intermediate to temporal hippocampus. A model of functional differentiation and integration along the septo-temporal axis of the hippocampus is proposed, describing key hippocampal contributions to adaptive behavior based on information encoded during a single or a few past experiences.

KEY WORDS

hippocampus, declarative memory, episodic memory, spatial learning and memory, locomotion, fear/anxiety, anterior/posterior hippocampus, dorsal/ventral hippocampus

1. INTEGRATING HIPPOCAMPAL FUNCTIONS

There is currently an immense interest in specific hippocampal[1] memory functions that may be relevant to human declarative, especially episodic, memory /1,43,72,73,121,151,155,171,172,186,187,191,210,212,220,241,242,259,262/. The multimodal sensory information thought to be critical for these memory functions is available to the hippocampus from the neocortex via the parahippocampal region, especially the entorhinal cortex /5,45,71,142,149,280,281/. In addition to memory functions, the hippocampus has also been associated with other functions, including emotion-

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[1] In this article, the terms 'hippocampal' and 'hippocampus' refer to the serially connected, cytoarchitectonically distinct regions dentate gyrus, cornu ammonis (CA) 1 to 3, and subiculum /5,6,8,281/. The cytoarchitectonic subfields of the hippocampus will mainly be treated as a cooperative unit; this is not meant to imply that these regions may not serve partly dissociable functions (see, e.g., /131/).

al /13,22,97/, motivational /57,62,258/, and sensorimotor functions /18,32,97,264/, to which it is linked via the prefrontal cortex and subcortical sites /5,6,280/. Interestingly, the connections to the entorhinal cortex and the links to prefrontal cortex and subcortical sites are differentially distributed along the hippocampal septo-temporal (or longitudinal) axis, running from the septal pole located closest to the septum to the temporal pole close to the temporal lobe[2] /5,199,216,250,279,280/ (Fig. 1); a corresponding functional differentiation along the septo-temporal axis of the hippocampus has become apparent over recent years /13,18,179,188, 235/. It should be noted, though, that neither the anatomical nor functional septo-temporal differentiation is absolute, but rather gradual, and that there are anatomical substrates for septo-temporal interactions, including longitudinal intrahippocampal fibers /5,7,38-40,119,150,194,234,235,280/.

The main purpose of the present paper is to argue that a key contribution of the hippocampus to adaptive behavior is the integration of (i) certain mechanisms of *rapid* learning with (ii) links to other behavioral functions, such as emotional, motivational, and sensoriomotor functions; thereby, behavior can be adjusted according to information encoded during single or a few experiences. Moreover, such functional integration within the hippocampus is suggested to involve interactions between anatomically and functionally differentiated parts that are distributed along the hippocampal septo-temporal axis. The mammalian hippocampus thus combines two fundamental, but contrasting properties of mammalian brain systems, functional differentiation of subregions and their integration in behavior /224,257,265/.

1.1. Outline of the article

This article focuses on the hippocampal contributions to behavior based on rapid place[3] learning. Place information, defining a location in a viewpoint-independent way, is a fundamental aspect of most everyday experiences, stored in so-called episodic memory /261/, and behavior based on rapid place learning is suitable for neurobiological studies in animals /2,42,43,87,182,186/. For example, tests have been developed for rats that are analogous to the problems of finding the location where one has parked a car or placed a key on a particular occasion. In these tasks, rats are required to find the location where they found food /17,89,116/ (also see Fig. 3A) or an escape from water /61,170,193,243,272/ on a single occasion in the past.

After pointing out that a common theme of many theories on hippocampal memory functions is the *rapid* encoding and subsequent retrieval of information, such as place information, from experience (Section 2), this review highlights some recent evidence concerning the underlying synaptic mechanisms within the hippocampus (Section 2.1). Importantly, as discussed below, slow incremental, in contrast to rapid, place learning might not absolutely require the hippocampus (Section 2.2). Evidence is then reviewed that the input of visuospatial information necessary for rapid place learning declines from the septal to the temporal pole of the hippocampus (Section 2.3). While this suggests a minor role for temporal parts of the hippocampus in place learning, it is important to realize that hippocampal mechanisms of rapid learning can only serve adaptive behavior via links to brain systems involved in the coordination and executive control of behavior (Section 3). As discussed below, these links decline from the temporal toward the septal pole of the hippocampus (Sections 3.1-3.4). Bringing the presented evidence and arguments together, a model is proposed that describes how different functions might be integrated along the septo-temporal axis of the hippocampus to support adaptive behavior based on the hippocampus-dependent rapid encoding of experience (Section 4).

2. HIPPOCAMPUS-DEPENDENT MEMORY REPRESENTATIONS

A common theme of many theories of hippocampal memory functions, supported by evidence

[2] A common alternative terminology for septal/temporal is dorsal/ventral in rodents and posterior/anterior in primates, including humans.

[3] In this article, place learning is used to refer to the acquisition of an allocentric or viewpoint-independent representation of a location /120,186/.

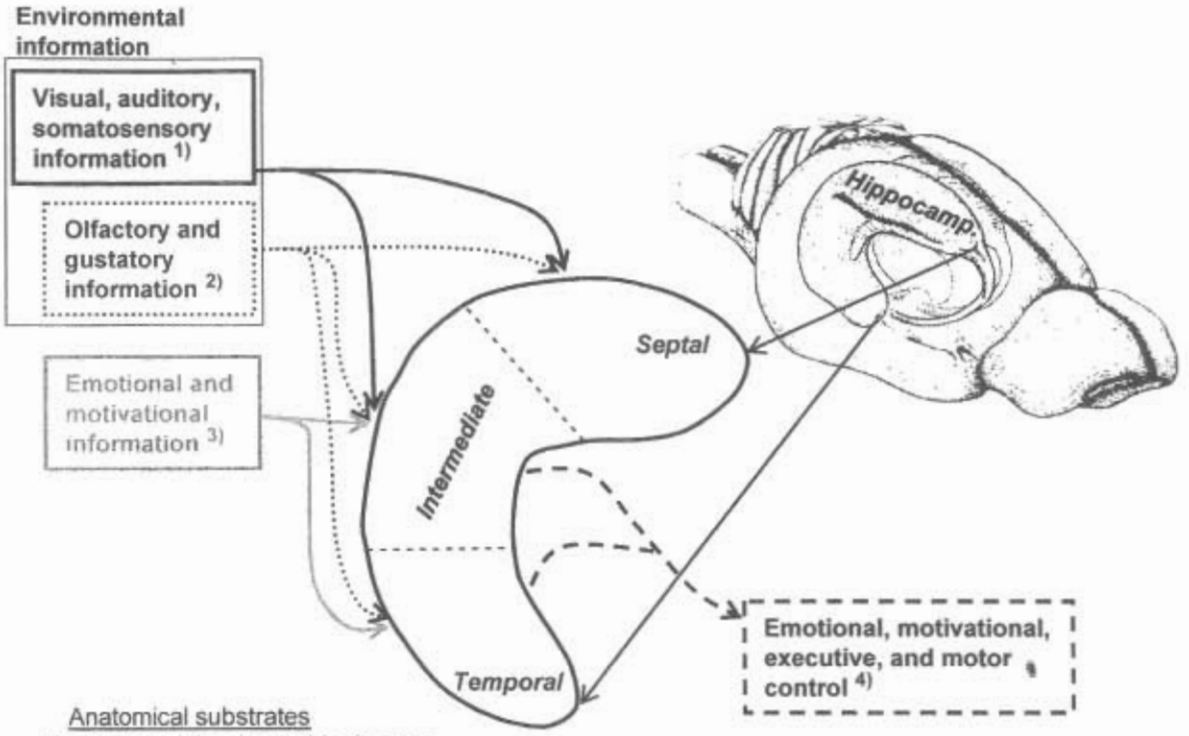


Fig. 1: Hippocampal links to different types of information and functions. The hippocampus, depicted in the rat brain, is linked to different types of environmental and internal state information (boxes on the left), as well as to many behavioral functions (box on the right) via its multitude of anatomical connections to cortical and subcortical sites (the list of anatomical substrates refers to the superscript numbers in the boxes). Importantly, the connectivity of the hippocampus is differentiated along this structure's septo-temporal axis, which runs from the septal pole, located close to the septum, to the temporal pole, located close to the temporal lobe. Connections to the dorso-lateral entorhinal cortex, which link the hippocampus to visual, auditory, and somatosensory information processed by the respective sensory neocortices, decline from the septal to the temporal pole and are mainly restricted to the septal and intermediate hippocampus. Only olfactory and gustatory inputs are distributed relatively evenly along the septo-temporal axis (further details and references are provided in the text, Section 2.3). Connections to the prefrontal cortex and subcortical sites, the main links to emotional, motivational, executive, and sensorimotor processes, decline from the temporal to the septal pole and are largely restricted to the temporal and intermediate hippocampus (further details and references are provided in the text, Sections 3.1 and 3.2).

across different lines of research in rodents, non-human primates, and humans, is the importance of the hippocampus for the rapid encoding and subsequent retrieval of memory representations conjoining features and their mutual relationships that define aspects of experiences /72,73,76,91, 107,120,151,156,158,163,165,171,172,183,186,191, 212,220,241,242,254,259,275,278/. Prominent examples of such representations include place memory, conjoining spatial features and their relationships, and the two subtypes of declarative memory, namely episodic memory, conjoining events and their spatio-temporal contexts into representations of unique episodes, and semantic memory, binding individual facts into a context of meanings.

2.1. Contributions of hippocampal synaptic plasticity and transmission

According to the views referred to above, sensory input representing a stimulus configuration, such as one that defines a place, mainly enters the hippocampus from the sensory neocortices via the entorhinal cortex /5,45,51,55,142,280,281/ and can rapidly be encoded into a memory representation by the induction of hippocampal synaptic plasticity mediated by NMDA receptors /33,160,173/. Subsequent retrieval of this memory can be triggered by sensory input from a part of the original stimulus configuration passing through the modified hippocampal synapses; this will result in reactivation of the hippocampal receptors /184/, and ultimately, it is assumed, the neocortical activity pattern originally evoked by the complete stimulus configuration ('pattern completion') (Fig. 2). These views imply that, at least temporarily, the memory is stored in the form of synaptic-weight changes in a hippocampal-neocortical network. A matter of intense debate is whether memories that depend on hippocampal synaptic plasticity and transmission for their encoding are permanently hippocampus-dependent for their storage and retrieval, or whether storage and retrieval become hippocampus-independent and solely dependent on the neocortex after a period of systems consolidation /70,85,171, 176,242/.

Supporting the suggested hippocampal mechanisms of rapid encoding and subsequent retrieval of certain memories, we demonstrated in rats that the rapid encoding of a place where food was found on one specific trial was impaired by blockade of hippocampal NMDA receptors mediating the induction of hippocampal long-term potentiation (LTP), a form of synaptic plasticity. Retrieval of the

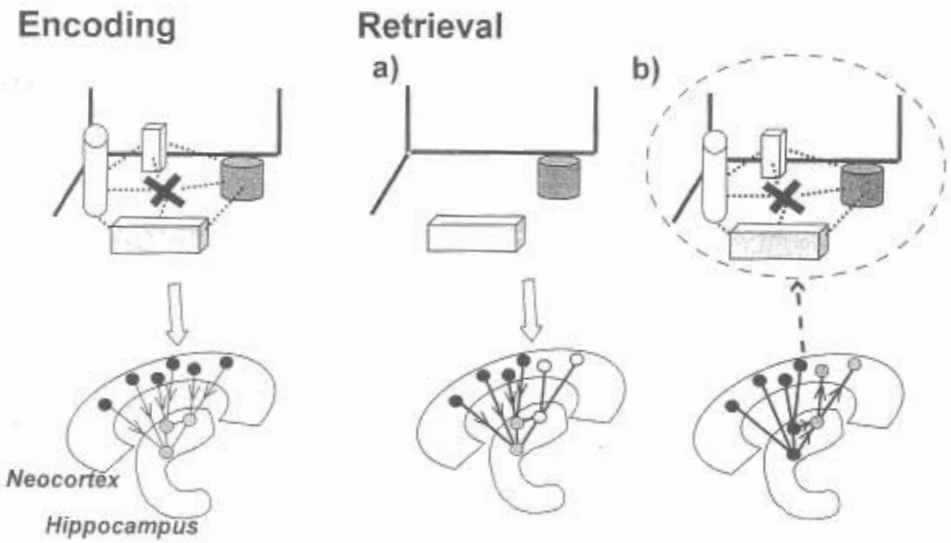


Fig. 2: A sketch of how the hippocampus is thought to contribute to the rapid encoding and subsequent retrieval of features and their relations. *Encoding:* A configuration of features, for example defining a place (cross), elicits a pattern of neuronal activity in the neocortex (black dots). The neocortical activity pattern stimulates a pattern of neuronal activity in the hippcampus (gray dots) and synaptic connections between involved neocortical and hippocampal neurons (thin black lines connecting the dots) are strengthened via mechanisms of synaptic plasticity, such as NMDA receptor-mediated LTP. *Retrieval:* a) Synaptic connections between the hippocampal and neocortical neurons have been strengthened (thick black lines) due to concurrent activity during encoding. Perception of a part of the feature configuration re-activates a part of the neocortical activity pattern (black dots) which re-activates a part of the hippocampal pattern (gray dots). b) Due to the strengthened neocortical-hippocampal and hippocampal-hippocampal synaptic connections (thick black lines), the original hippocampal and neocortical activity patterns get completed (black and gray dots), resulting in a neuronal representation of the complete original feature configuration and the place (gray oval).

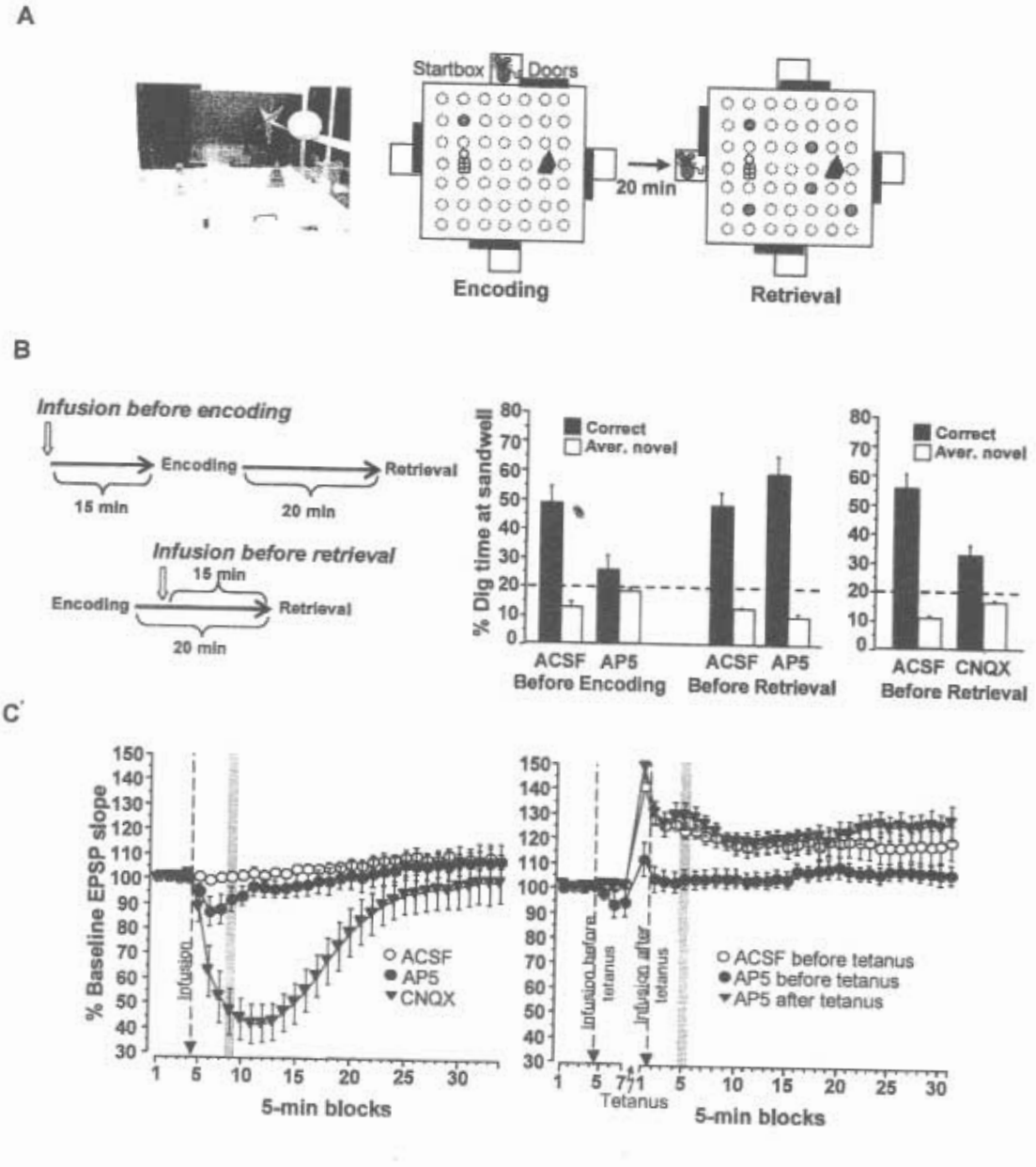
rapidly encoded place memory was not affected by the NMDA receptor blockade, but impaired by hippocampal blockade of AMPA/kainate receptors mediating fast excitatory transmission through hippocampal synapses /17/ (Fig. 3). Distinct effects of hippocampal NMDA and AMPA receptor blockade on memory encoding and retrieval were also found in a task requiring rats to remember paired associates consisting of a flavor and the place where food of this flavor was found on a specific trial /64/. Also, context fear conditioning, the conditioning of fear responses to an environment (the conditioning 'context') where rats or mice received electric foot-shocks is dependent on hippocampal NMDA receptors; in contrast, fear conditioning to a tone paired with foot-shocks does not require hippocampal NMDA receptors, consistent with a role of these receptors in encoding memory representations of stimuli and their relationshps, namely those that compose the conditioning context /21,208,247,286,289/. Importantly, the contributions of hippocampal NMDA receptors are not restricted to memory with a spatial component. For example, NMDA receptor blockade in the hippocampus impaired the rapid encoding of socially transmitted food-preference in rats, a non-spatial form of memory thought to involve the representation of relationships between features of an experience /218/. Furthermore, NMDA receptor-mediated mechanisms in the hippocampus appear not to be required for the encoding of short-term or working memory, as rats with blockade of hippocampal NMDA receptors can encode a place memory and retrieve it after a retention delay of about 15 s /243/ (see also /144/). Given that such short-term memory is disrupted in rats with hippocampal lesions /19,128,243/, it still depends on the hippocampus, though possibly on NMDA receptor-independent reverberatory synaptic transmission through hippocampal circuits /141/.

2.2. Rapid versus incremental learning

In contrast to the critical hippocampal contributions to the rapid encoding and subsequent retrieval of certain memories, including place memory (see above), rats and mice can incrementally, i.e. slowly over many trials, encode accurate place information and later retrieve it despite impaired hippocampal LTP /11,12,111, 174,192,214,225,226/. Indeed, the hippocampus overall seems to be relatively dispensable for such slow incremental learning. For example, the famous patient, H.M., who had parts of his temporal lobe, including large portions of the hippocampus, removed to stop seizures, very slowly learnt accurate place information after the surgery /58/ (Fig. 4), while rapid place learning is strongly impaired in H.M. and other patients with extensive hippocampal damage /43,112,133,195, 237,238,245/. Similar to the spatial learning abilities spared in H.M., rats with complete hippocampal lesions (sparing the subiculum) can slowly and incrementally learn accurate place information over many trials /19,116,175,273/.

Specific contributions of the hippocampus to the rapid acquisition of information about stimuli and their relationships are also suggested by experiments recording hippocampal activity during exposure to novel places in rats and over the course of paired-associates learning tasks in humans and monkeys. Firing of neurons in the rat hippocampus can come to represent novel places very rapidly, within as little as 5 s, as reflected by place-specific firing /84/. Moreover, electrophysiological recordings in macaques /276/ and functional neuroimaging experiments in humans /68,288/ revealed that hippocampal activity changes rapidly during the initial encoding and retrieval of paired associates (location-scene pairs in the macaques, face-name pairs or object-position pairs in the human studies). The neuroimaging studies in humans further revealed that activation in a neocortical area (the frontal cortex) increased incrementally when the paired associates were presented repeatedly over many trials..

All these findings are in line with suggestions that the hippocampus is only critical for the *rapid* encoding and subsequent retrieval of memory for stimuli and their relationships, while neocortical areas may support slow incremental learning and subsequent retrieval of such information to some extent. It has been argued that the existence of such 'complementary learning systems' is plausible because the neuro-computational requirements for rapidly encoding details of a specific experience are


A
Startbox
Doors
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20 min
% Dig time at sandwell
Correct
Aver. novel
ACSF AP5
Before Encoding
ACSF AP5
Before Retrieval
ACSF CNQX
Before Retrieval
C
% Baseline EPSP slope
Infusion
ACSF
AP5
CNQX
5-min blocks
Infusion before tetanus
Infusion after tetanus
ACSF before tetanus
AP5 before tetanus
AP5 after tetanus
Tetanus
5-min blocks

Fig. 3: **Distinct contributions of hippocampal NMDA and AMPA receptors to encoding and retrieval of one-trial place memory. A.** *One-trial place memory task in the event arena:* The event arena (photograph and sketches) has a 7x7 grid of circular holes covered by lids that can be removed to insert sandwells. A trial (sketches) comprises an encoding and retrieval phase separated by a retention delay of 20 min. In the encoding phase, the rat must search for food reward (white dot) buried in a sandwell (filled circle) in a trial-specific place; all other possible sandwell locations (stippled circles) are closed and covered by sawdust. In the retrieval phase, food is buried in a sandwell in the same place as in the encoding phase, and sandwells without food are open in four novel places; in order to find food efficiently in the retrieval phase, the rat must use one-trial place memory according to a win-stay rule. Start positions for encoding and retrieval phases are different requiring allocentric place memory. (Adapted from /17, Fig. 1/.) **B.** *Effects of hippocampal infusion of the NMDA receptor antagonist AP-5 or the AMPA receptor antagonist CNQX on encoding and retrieval:* AP-5 (30 mM, 1 µl/side), CNQX (3 mM, 1 µl/side), or, as control, the infusion vehicle (artificial cerebrospinal fluid [ASCF]) were bilaterally infused into the posterior septal hippocampus 15 min before encoding (left panel, top) or 15 min before retrieval (left panel, bottom) of probe trials. In probe trials, neither the correct nor the novel sandwells contained food during the retrieval phase, and dig time at the different sandwells was recorded during 60 s as measure of one-trial place memory. The bar diagrams (middle and right panels) represent the percentage of dig time (mean + 1 SEM) at the correct and novel sandwells for the different infusion conditions, with the stippled horizontal lines indicating chance level. NMDA receptor blockade disrupted encoding, but not retrieval (middle panel): When AP-5 was infused before encoding, dig time at the correct well was reduced compared to ACSF infusion and did not differ from chance (left part), while AP-5 infusion before retrieval did not affect performance (right part). In contrast, AMPA receptor blockade disrupted retrieval (right panel): CNQX infusion before retrieval reduced dig time at the correct sandwell as compared to ACSF infusion. (Adapted from /17, Fig. 3/.) **C.** *Effects of hippocampal AP-5 and CNQX infusions on synaptic transmission and plasticity:* Extracellular postsynaptic potentials (EPSPs) in the dentate gyrus evoked by low-frequency stimulation of the perforant path, which carries fibers from the entorhinal cortex, were recorded in anesthetized rats. Data are presented in 5-min blocks as percentage of the average EPSP slope during the 20-min baseline recordings preceding the first infusion (% baseline EPSP slope, mean + 1 SEM). Artificial cerebrospinal fluid (ACSF, 1 µl), D-AP-5 (30 mM, 1 µl), or CNQX (3 mM, 1 µl) were infused at the times indicated by the arrows. Only CNQX, but not AP-5, infusion significantly reduced basal (low-frequency) synaptic transmission (left panel). The vertical gray bar indicates 15-20 min after infusion, corresponding to the time during which the encoding or retrieval phase took place after the hippocampal infusions in the behavioral experiment. AP-5 infusions selectively blocked the induction (infusions before tetanus), but not maintenance (infusions after tetanus), of LTP. The gray bar indicates 20-25 min after tetanization, corresponding to the delay between encoding and retrieval in the one-trial place task. (Adapted from /17, Fig. 5/.)

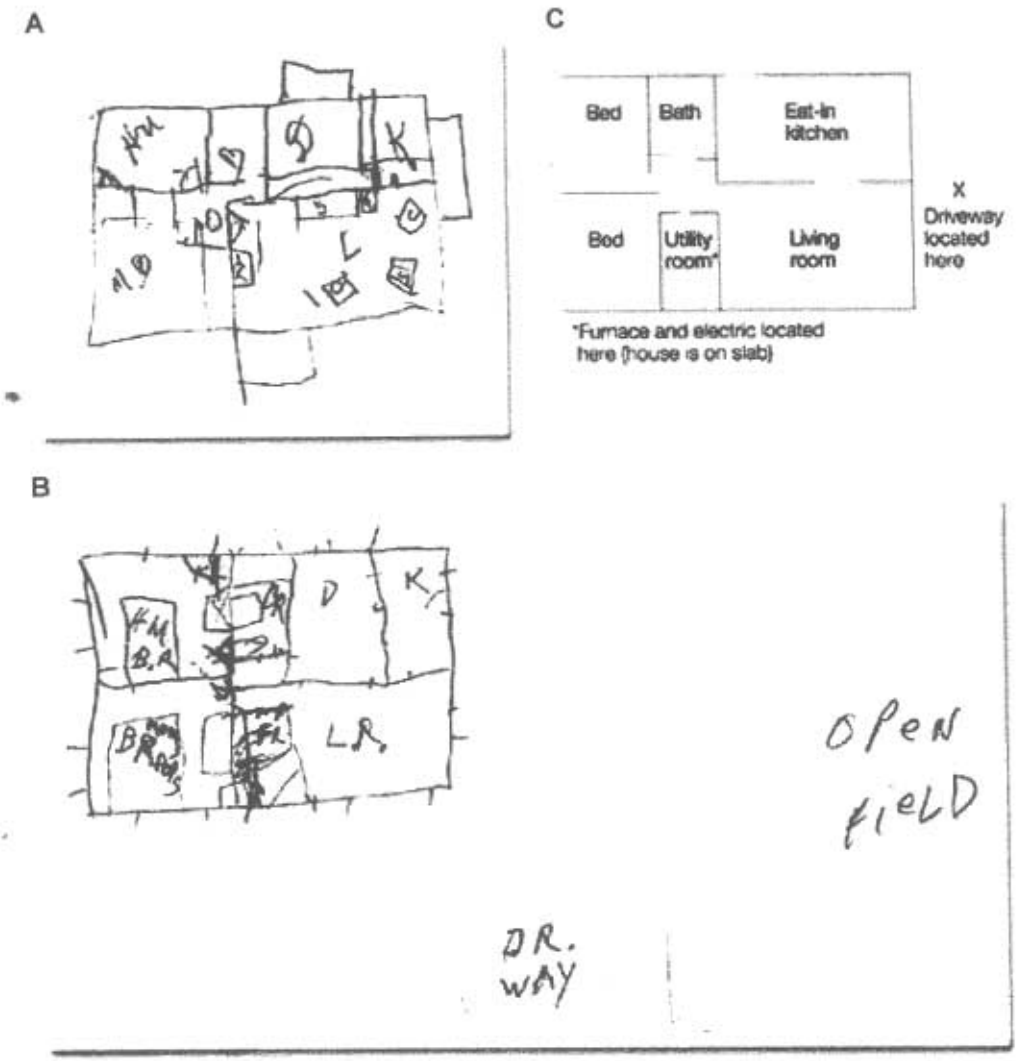

Fig. 4: **Incremental place learning by patient H.M. after the bilateral resection of his medial temporal lobes.** In 1953, patient H.M.'s medial temporal lobes, including the hippocampus, were resected bilaterally to stop seizures. The figures show floor plans H.M. drew of the house he had never seen before his operation, but where he was living from 1958-1974, allowing for slow incremental learning of the spatial layout. **A.** Drawing prepared in 1966 (B = bathroom; C = chair; D = dining room; HM = H.M.'s bedroom; K = kitchen; L = living room; MB = Mom's bedroom; TV = television); **B.** Drawing prepared in 1977 (3 years after H.M. had moved out, thus demonstrating persistent long-term memory (BR = bathroom; D = dining room; FR = furnace room; HM B.R. = H.M.'s bedroom; K = kitchen; L.R. = living room; Mom & Dad's BR = Mom and Dad's bedroom). **C.** Current floor plan of the house (the wall between kitchen and dining room was taken down by a recent owner to make an eat-in kitchen). (Adapted from /58, Fig. 2/.)

incompatible with those for extracting generalities from many experiences /163,190,191/.

Interestingly, a relative sparing of semantic as compared to episodic memories in patients with selective hippocampal damage /58,227,262,266, 267/ may relate to hippocampal mechanisms being required for the rapid, but not for the slow incremental, encoding of certain types of information. Semantic memory can often benefit from many repeated learning events while episodic memory is,

by definition, based on single encoding events /261/. However, another reason for the particular importance of the hippocampus in episodic memories may be this structure's role in associating events across time to create the memory for sequences of events that compose episodic memories /49,69,74,83,128-130,132,151,210,231/.

2.3. Septo-temporal differentiation of hippocampal contributions to place memory

Hippocampal access to sensory information, except for the olfactory and gustatory modalities /138,139,199,219/, is largely provided by projections from the dorso-lateral band of the entorhinal cortex, and these projections decline from the septal to the temporal pole /5,45,280/ (compare Fig. 1). In line with this anatomical arrangement, neurons in the septal hippocampus and the associated dorso-lateral part of the medial entorhinal cortex show strong modulation by visuo-spatial information, whereas this modulation decreases toward the temporal hippocampus and the associated ventro-medial aspects of the medial entorhinal cortex /56,86,102,105,125,135,136,162, 207,209/ (Fig. 5). Thus, the hippocampal involvement in the encoding and retrieval of memory representations based on visuo-spatial information may decline from the septal to the temporal pole.

Several studies have found that performance on place learning tasks was more impaired after septal hippocampal lesions than after temporal lesions of comparable size (reviewed in 13,179/). The most striking finding was that, after 32 training trials (8 trials/day for 4 days), to a hidden escape platform in the watermaze, rats with partial hippocampal lesions sparing only 20-40% of hippocampal volume ('minislabs') at the septal pole showed similar memory for the platform location as control rats, while rats with even 40-60% spared hippocampal volume at the temporal pole were substantially impaired /180/ (see also /177/). However, a systematic replication and re-examination /66/ demonstrated that the superiority of septal as compared to temporal hippocampal tissue is dependent on the training protocol. A slight alteration of the training protocol (increased trial spacing, 4 trials/day for 8 days) enabled rats with 20-40% sparing at either the septal or the temporal pole to show place memory similar to control rats after 32 trials. Moreover, several studies have found significant impairments in the acquisition of place memory tasks in rats with 30-50% of hippocampal volume spared at the septal pole /19,36,66,67,77,78/. Also, when rats had learned a place task in the watermaze with an intact hippocamppus, relatively small hippocampal lesions sparing the septal 60-70% of the structure impaired subsequent task performance /178/. This is consistent with cellular imaging data from rats /101/ and functional imaging data from humans /98/, suggesting that in the intact hippocampus a large septo-temporal network is normally recruited by place and episodic learning tasks.

In this context, it is important to note that place memory is hippocampus-dependent especially for its rapid acquisition, while incremental place learning may ultimately be achieved without a hippocampus (see Section 2.2 and Fig. 4). Indeed, there is evidence that behavior based on one-trial, i.e. very rapid, place learning in the watermaze is impaired by hippocampal lesions sparing 40-50% volume at either the septal or temporal pole /19,78/. Thus, even though the accuracy of hippocampal place representations declines from the septal to the temporal pole, behavioral performance based on hippocampus-dependent rapid place learning appears to require the contributions of a septo-temporally distributed hippocampal network. The next part of this paper discusses possible reasons for this.

3. FROM HIPPOCAMPUS-DEPENDENT RAPID PLACE LEARNING TO ADAPTIVE BEHAVIOR: A CRITICAL ROLE FOR THE TEMPORAL TO INTERMEDIATE HIPPOCAMPUS?

After encoding and subsequent retrieval, how is hippocampus-dependent memory related to emotional, motivational, executive, and motor control sites, so that it can serve adaptive behavior (also compare /207,213,232/)? Based on anatomical and functional evidence, which is reviewed in the following paragraphs, it is likely that more temporal parts of the hippocampus make substantial contributions to such translation of hippocampus-dependent memory into adaptive behavior.

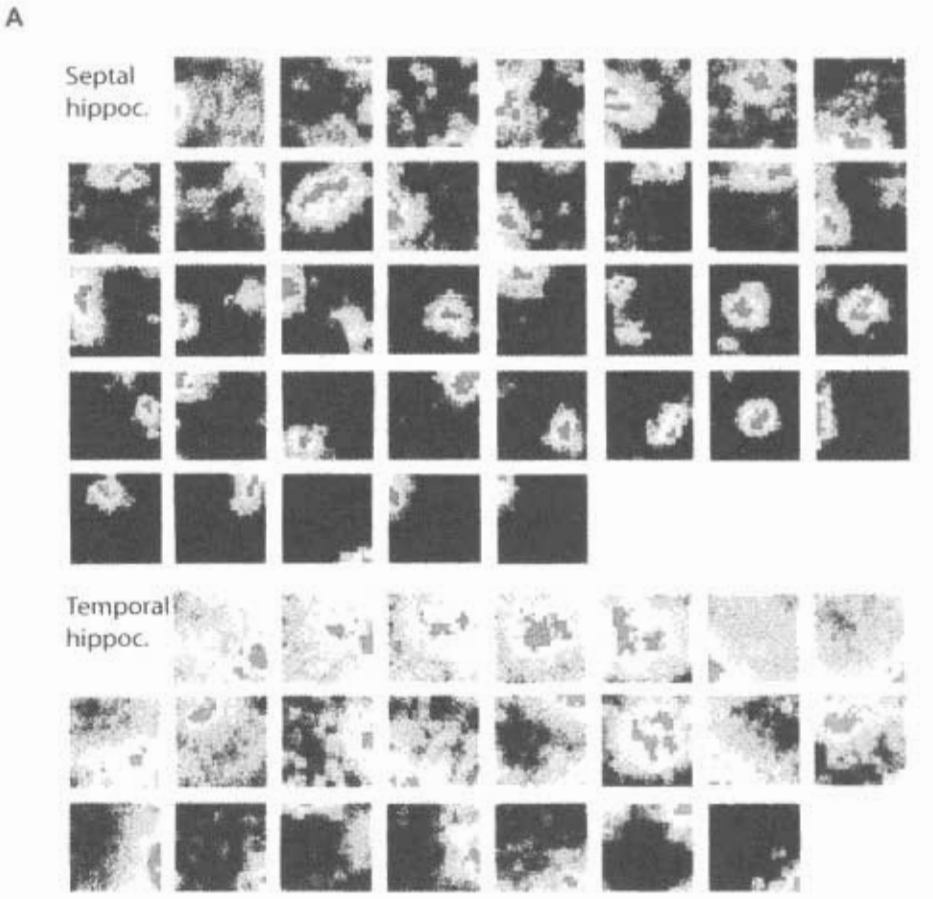
A
Septal hippoc.
Temporal hippoc.
B
Medial entorhinal cortex
Hippocampus
Septal
Temporal
Dorso-lateral
Ventro-medial
C
Medial entorhinal cortex
Dorso-lateral
Inter-mediate
Ventro-medial

Fig. 5: Differential spatial modulation of cell firing along the septo-temporal axis of the hippocampus and the dorsolateral-to-ventromedial axis of the medial entorhinal cortex. A. *Spatial firing maps of cells in the septal and the temporal hippocampus.* The spatial distribution of firing rates in square-shaped environments is depicted for individual CA1 pyramidal cells in the septal (top) and temporal (bottom) hippocampus; recording sites corresponded to about 20% and 65%, respectively, along the septo-temporal axis. Black background indicates no firing, dark gray centers of the firing fields indicate maximum firing rate, and the gray-shade bands around the center indicate the gradual decrease in firing rate toward the periphery of the firing fields. Note that cell firing in the septal hippocampus is much more spatially restricted than in the temporal hippocampus. In addition, 45% (39/83) of recorded pyramidal cells in the septal hippocampus had place fields, whereas only 18% (27/134) of the temporal pyramidal cells showed place fields. (Adapted from /125, Fig. 4./) **B.** *Septo-temporal topography of projections from the dorso-lateral and ventro-medial bands of the medial-entorhinal cortex to the hippocampus.* Sagittal brain sections showing the injection sites of an anterograde tracer in the dorso-lateral (left, top) and ventro-medial (left, bottom) band of the medial entorhinal cortex, as well as the resulting anterograde staining in the dentate gyrus (upward white arrow in high-power darkfield photograph) and CA1 (downward white arrow in high-power darkfield photograph) of the septal and temporal hippocampus (hippocampal cytoarchitectonic subfields are indicated: DG = dentate gyrus; CA1 and CA3 = subfields CA1 and CA3; S = subiculum). The dorso-lateral band projects heavily to the septal, but not the temporal, hippocampus, while the ventro-medial band only projects moderately to the temporal hippocampus. (Adapted from /86, Fig. 1/.) **C.** *Spatial firing maps of cells in the dorso-lateral, intermediate, and ventro-medial bands of the medial entorhinal cortex.* The spatial modulation of firing rates of individual cells, depicted for square-shaped environments, decreases from the dorso-lateral to ventro-medial band, where cell firing virtually does not show any spatial restriction. Gray-shade coding of firing rates is as explained for A. (Adapted from /86, Figs. 2 and 3/.)

3.1. Septo-temporal differentiation of the hippocampal connectivity with the prefrontal cortex and subcortical nuclei

The hippocampus is linked to emotional, motivational, executive, and motor control mainly via the temporal and intermediate hippocampus that have strong direct connections to the prefrontal cortex /14,79,93,122,123,248,255,269/ and to subcortical sites, such as the amygdala /199,205/, nucleus accumbens /99,127,168/, septum and hypothalamus /54,134,199,216/ (Fig. 1). These connections are mainly to the CA1 subregion and the subiculum, and they are all reciprocal, except for the connections to the nucleus accumbens and prefrontal cortex, which consist only of hippocampal projections /5,280/.

The prefrontal cortex and the subcortical sites link the hippocampus to brainstem sites mediating motor responses /4,113,168/. Furthermore, the prefrontal cortex plays a central role in executive functions, required for the efficient organization of complex and temporally extended behavior and including attention, working memory, response control, planning, and guidance of behavior based on previously learned rules /94,166,217,222,274, 282,283/. In addition, the prefrontal cortex, the amygdala, and the nucleus accumbens play key roles in the emotional and motivational control of behavior /28,52,60,63,143,157,200-202,277/. Finally, the hypothalamus, to which the hippocampus is connected both directly and via the lateral septum /54,134,199,216/, regulates basic behaviors, serving defense, food intake, locomotion, and reproduction, and has been suggested as the central interface to coordinate forebrain influences on brainstem centers that generate motor patterns /249/.

3.2. Modulation of meso-corticolimbic dopamine transmission by the temporal to intermediate hippocampus: a substrate for hippocampal influence on many aspects of behavioral control?

Importantly, via its projection to the prefrontal cortex and subcortical sites, the temporal to intermediate hippocampus is polysynaptically linked to the ventral tegmental area (VTA), the origin of the mesocortico-limbic dopamine system /53,152,204, 255,263/. This system innervates many parts of the forebrain, including the prefrontal cortex, the nucleus accumbens, the amygdala, and also the hippocampus /147/. The behavioral significance of dopamine release depends on the target structure, but overall the meso-corticolimbic dopamine system plays an important role in many aspects of behavior, including the modulation of attentional, emotional, motivational, and sensorimotor processes /20,26-29,80,95,114,118,147,152,168,200-202, 217,228,277/.

Consistent with anatomical connections, stimulation of the temporal half of the hippocampus polysynaptically modulates activity of neurons in the VTA /82,145,153/ and reversibly increases tonic dopamine release in the nucleus accumbens /30,35,37,115,145,167,196/ and the medial prefrontal cortex /100,197/, while the effects in other projection targets of the VTA remain to be examined. Moreover, temporary pharmacological inactivation of the temporal hippocampus reversibly reduces the accumbal dopamine response to novelty /146/. In contrast to temporal hippocampal stimulation, stimulation of the septal hippocampus does not have a stimulatory effect on accumbal dopamine transmission /115,196/ (Fig. 6).

3.3. Behavioral functions preferentially associated with the temporal half of the hippocampus

In addition to the anatomical and functional connectivity reviewed above, there is direct evidence that some of the behavioral responses to which the hippocampus-dependent memory might need to be related are preferentially associated with the temporal half of the hippocampus. First, in the watermaze and in context fear conditioning, and generally when places have been associated with the refuge from or the exposure to aversive situations during a past experience, it is important that rapidly encoded place information is translated into appropriate protective responses. Many such protective responses, or fear/anxiety-related behaviors, have been found to be disrupted by lesions or temporary inactivation of the temporal, but not septal, half of the hippocampus /10,13,23,31,44, 65,137,154,156,181,198,215,260/ (Fig. 7). Second, locomotion is often vital for the use of place information: we walk to the place where we

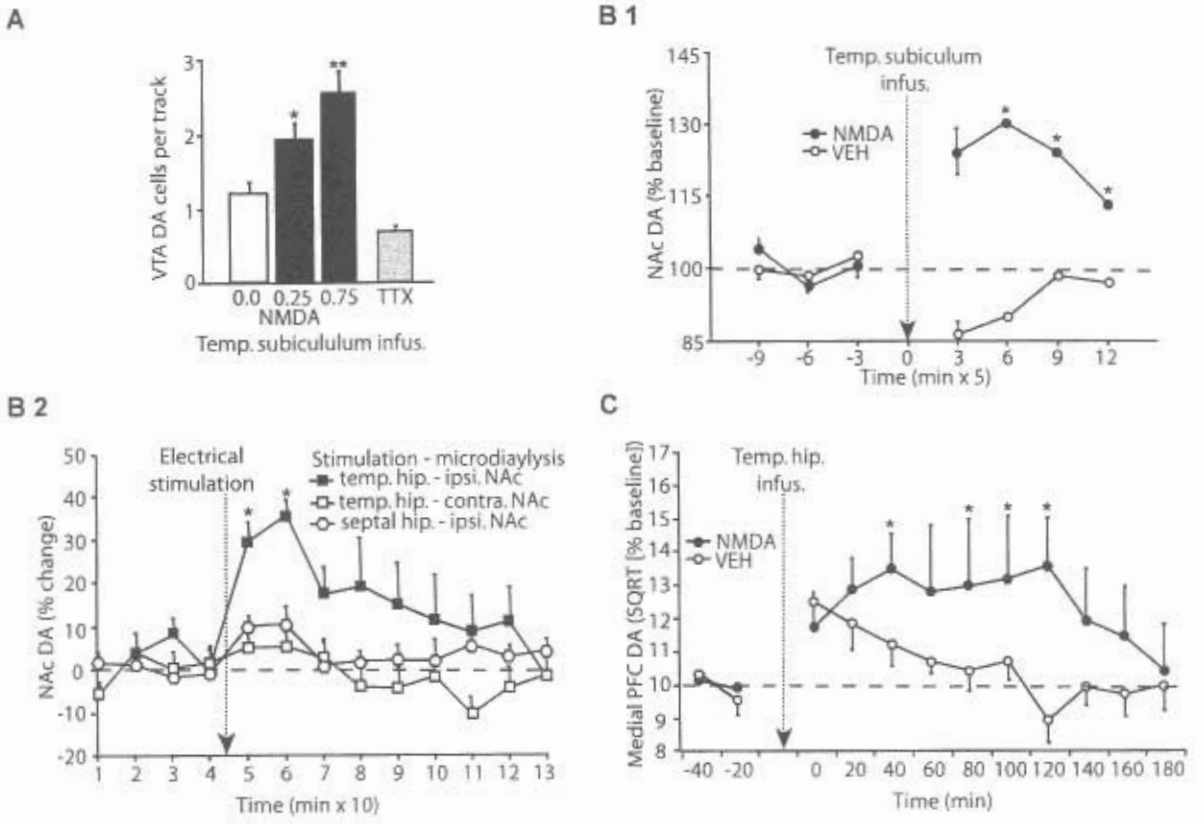

Fig. 6: **Modulation of the mesocortico-limbic dopamine system by the temporal half of the hippocampus. A.** *The temporal hippocampus positively modulates firing of dopaminergic neurons in the ventral tegmental area.* Unilateral NMDA stimulation of the temporal subiculum (0.25, 0.75 µg/0.5 µl) increased the number (mean + 1 SEM) of spontaneously firing dopamine (DA) cells in the ventral tegmental area (VTA), as compared to the control group (0.0 µg NMDA), while TTX inactivation (1 µM, 0.5 µl) decreased this number, even though non-significantly ($p > 0.10$). Asterisks denote significant differences (* $p < 0.05$, ** $p < 0.01$) as compared to the control group (0.0 µg NMDA). (Adapted from /82, Fig. 2/.) **B.** *Stimulation of the temporal hippocampus increases dopamine transmission in the nucleus accumbens. B1.* Unilateral infusion of NMDA (2 µg/0.5 µl), as compared to infusion of the drug vehicle (VEH) alone, into the temporal subiculum increased levels of dopamine (DA; depicted as percentage of pre-infusion baseline, mean + 1 SEM) in microdialysates from the ipsilateral nucleus accumbens (NAc). Stippled line corresponds to 100% baseline. Asterisks indicate significant differences from the pre-infusion baseline values ($p < 0.05$). (Adapted from /37, Fig. 4/.) *B2.* Unilateral electrical stimulation (0.5 ms, 300 µA current pulses, 20 Hz, 10 s; arrow) of the temporal hippocampus increased DA levels (depicted as % change compared to pre-stimulation baseline, mean + 1 SEM) in the ipsilateral, but not contralateral, NAc, while stimulation of the septal hippocampus was without effect. Stippled line corresponds to 0% change. Asterisks denote a significant difference from baseline ($p < 0.05$). (Adapted from /115, Fig. 4/.). **C.** *Temporal hippocampal NMDA stimulation increases dopamine release in the medial prefrontal cortex.* Unilateral infusion of NMDA (0.5 µg/0.5 µl), as compared to vehicle (VEH), into the temporal hippocampus increased DA levels (presented as SQRT of the percentage of the average concentration in the two baseline samples, mean + 1 SEM) in microdialysates from the ipsilateral medial prefrontal cortex (PFC). Time points indicate the beginning of the dialysate samples with respect to the start of the infusion. Stippled line corresponds to 100% baseline. Asterisks indicate significant differences between the NMDA and VEH group ($p < 0.05$). Note: following infusion, DA in the medial PFC increased in both groups as compared to baseline; this is likely to reflect handling of the rats during the infusion. (Adapted from /197, Fig. 4/.)

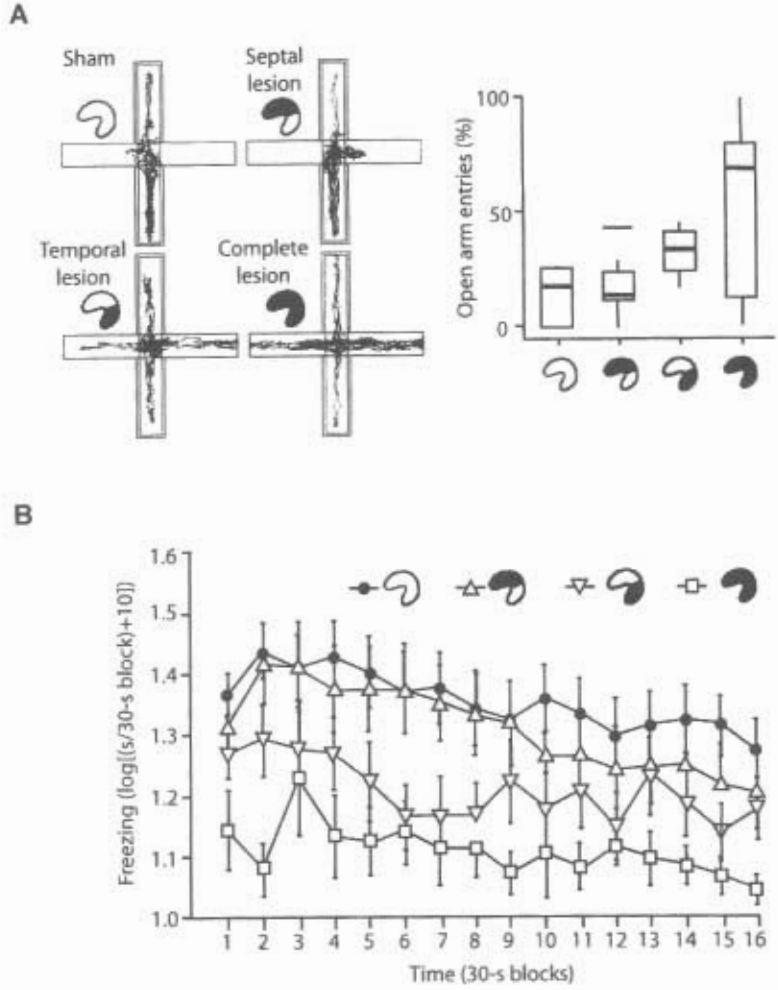

Fig. 7: **Septo-temporal differentiation of the hippocampal contributions to innate and conditioned fear/anxiety. A.** *Preferential role of the temporal hippocampus in an innate fear/anxiety response (open-arm avoidance on the elevated-plus maze).* Complete or temporal, but not septal, hippocampal lesions (approximate average spared volume of hippocampus, except subiculum: 4%, 46%, or 25%, respectively) reduced open-arm avoidance on the elevated plus maze, a normal innate fear/anxiety response. Shown are: left, representative paths of rats in the different experimental groups during a 10-min test session on the maze, with double contours indicating closed arms; right, median percentage of visits to open arms (with interquartile distances, upper and lower limits, and outliers) in the different groups: rats with temporal hippocampal lesions had a significantly higher percentage of visits to open arms than rats with sham and septal-hippocampal lesions; they were not different from rats with complete hippocampal lesions, nor did the sham and septal-hippocampal lesion groups differ. (Adapted from /137, Fig. 2/.) **B.** *Preferential role of the temporal hippocampus in conditioned fear to an elemental cue.* Complete or temporal, but not septal, hippocampal lesions (estimated spared volume of hippocampus, except subiculum: virtually none, about 50-55%, or 45%, respectively) before conditioning sessions, during which rats were presented with tone-shock pairings, reduced conditioned fear, as reflected by freezing, during presentation of the tone in a subsequent test session. Conditioned freezing during the 8-min tone presentation is presented as the logarithmic transformation of the number of seconds spent per 30-s block (mean + 1 SEM). Both complete and temporal hippocampal lesions reduced freezing as compared to the sham group; in addition, the septal-, but not temporal-, hippocampal lesion group exhibited significantly more freezing than the complete-hippocampal lesion group. (Adapted from /215, Fig. 2B/.)

remember that we parked our car or left our keys; rats move to the place where they remember they found food or escaped from water during a previous occasion. As compared to the septal hippocampus, the temporal half of the hippocampus is more closely associated with the modulation of some sensorimotor processes, including locomotion /18/. A very striking example is the difference between the effects of septal and temporal hippocampal stimulation by NMDA: NMDA infusions into the temporal hippocampus dose-dependently increase locomotion, while septal hippocampal NMDA stimulation has virtually no effect /290/ (Fig. 8). In contrast to stimulation, temporary inhibition of neuronal activity in the temporal hippocampus decreases locomotion /23/.

Both fear/anxiety /200,202,270/ and locomotion /3,20,27,118,169,239,246/ may depend on dopamine transmission in the prefrontal cortex and nucleus accumbens, and the drive of locomotion by stimulation of the temporal hippocampus is prevented by systemic treatment with dopamine antagonists /15,24,35,253/ or by destruction of dopaminergic forebrain projections from the VTA /284/. This indicates that the preferential role of the temporal, as compared to the septal, hippocampus in fear/anxiety and locomotion may partly be related to the influence of the temporal hippocampus on the mesocorticolimbic dopamine system.

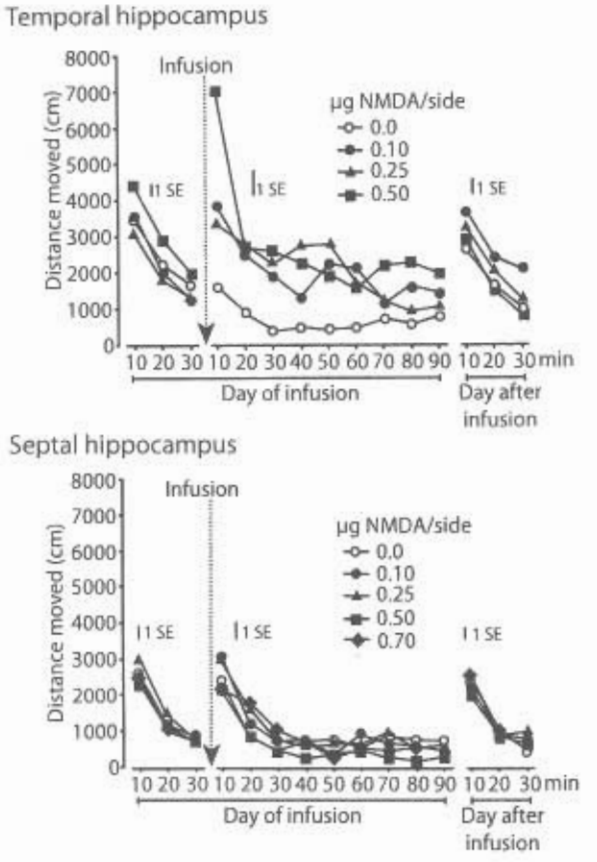

Fig. 8: Septo-temporal differentiation of the hippocampal modulation of locomotion: temporal, but not septal, hippocampal NMDA stimulation increases locomotion. Bilateral infusion of NMDA into the temporal (top), but not septal (bottom), hippocampus dose-dependently and temporarily increased locomotion in an open field. Locomotion is presented as the mean of the total distance moved during a 10-min block, with the variance indicated by 1 SE derived from the analysis of variance. (Adapted from /290, Fig. 2/.)

3.4. Interactions between hippocampus and prefrontal-subcortical circuits in behavior based on rapid place learning

Electrophysiological recording studies in rats revealed that hippocampal neuronal activity entrained neuronal firing in the prefrontal cortex /117, 124,233/ and nucleus accumbens /159,251/ during foraging behavior that required the rapid encoding and subsequent use of place information. In view of the topography of hippocampal connections (Section 3.1; Fig. 1), these interactions are likely to be mediated by the temporal to intermediate hippocampus. Furthermore, there is some intriguing direct evidence that interactions of the hippocampus with the prefrontal cortex and nucleus accumbens are involved in the efficient foraging behavior of rats based on trial-specific place memory in radial-arm maze tasks /81,230/. Transient disconnection of the hippocampus from the medial prefrontal cortex or the nucleus accumbens was achieved using lidocaine infusions into the temporal hippocampus on one side of the brain and into the prefrontal cortex on the other /81/. Moreover, the effect of transient hippocampal disconnection from prefrontal dopamine transmission was investigated using crossed infusions of lido-

caine into the temporal hippocampus and of a D_1 receptor antagonist into the prefrontal cortex /230/.

The delayed win-shift task consists of an encoding phase in which four out of eight maze arms are baited with food, followed, 30 min later, by a retrieval phase with food in those four arms that were unbaited during encoding. Efficient foraging during the retrieval phase was disrupted by hippocampal-prefrontal disconnection /81/, as well as by hippocampl disconnection from prefrontal D_1 receptor transmission /230/ during the retrieval, but not during the encoding phase. Disconnection of hippocampus and nucleus accumbens was without effect on this task /81/. In contrast, another task, the non-delayed foraging task, was disrupted by hippocampo-accumbal disconnections, but unaffected by hippocampo-prefrontal disconnections /81/. In this task, four arms are randomly baited each day, and efficient foraging requires rats to enter arms in a non-repetitive manner using the trial-unique memory of the already entered arms. Why did the manipulations have different effects on the delayed and non-delayed task? It was suggested /81/ that during the retrieval phase of the delayed win-shift task, rats forage according to a prospective strategy that is based on trial-unique place memory and that involves hippocampo-prefrontal interactions. In contrast, the non-delayed random foraging task may not involve a prospective strategy and, under these circumstances, the direct translation of trial-unique place memory into appropriate foraging behavior may involve hippocampo-accumbal interactions.

4. FROM THE RAPID ENCODING OF EXPERIENCE TO ADAPTIVE BEHAVIOR: A MODEL OF FUNCTIONAL DIFFERENTIATION AND INTEGRATION ALONG THE SEPTO-TEMPORAL AXIS OF THE HIPPOCAMPUS

The evidence and arguments described in the preceding paragraphs suggest that a network distributed along the septo-temporal axis of the hippocampus may be critical to enable adaptive behavior based on environmental information, such as place information, encoded rapidly during single or a few experiences. Key aspects of the hippocampal contributions to such behavior may be described by the following functional-anatomical model (Fig. 9):

1. The hippocampus has access to environmental information from the sensory neocortices. The *rapid*, but not incremental, encoding of environmental stimuli and their relationships into lasting memory representations requires the induction of hippocampal synaptic plasticity, while the subsequent retrieval of these representations is mediated by transmission through the modified hippocampal synapses. Sensory inputs, with the exception of olfactory and gustatory information, arrive mainly via the dorso-lateral entorhinal cortex to modulate neuronal activity in the septal to intermediate hippocampus. Therefore, the septal to intermediate regions play a predominant role in the rapid encoding and subsequent retrieval of environmental information by the hippocampus.
2. The hippocampus can interact with emotional, motivational, executive, and motor control processes. This interaction is mainly mediated by the temporal to intermediate hippocampus that is intimately linked to the prefrontal cortex and subcortical sites and exerts a positive modulation of the meso-corticolimbic dopamine system.

Thus, the hippocampus combines the substrates necessary to rapidly encode and subsequently retrieve environmental information with links to emotional, motivational, executive, and motor control processes that can enable the translation of this information into adaptive behavior. As different functions are distributed along the septo-temporal axis, the translation of hippocampus-dependent memory representations into appropriate behavior is likely dependent on an additional aspect of hippocampal organization, namely:

3. The septo-temporal differentiation of function within the hippocampus is complemented by anatomical and physiological features that allow for the integration of functions along the septo-temporal axis of the hippocampus. While these features remain to be clarified, there are several candidates. First, as the anatomical septo-temporal differentiation of the hippocampus is gradual, there is substantial overlap

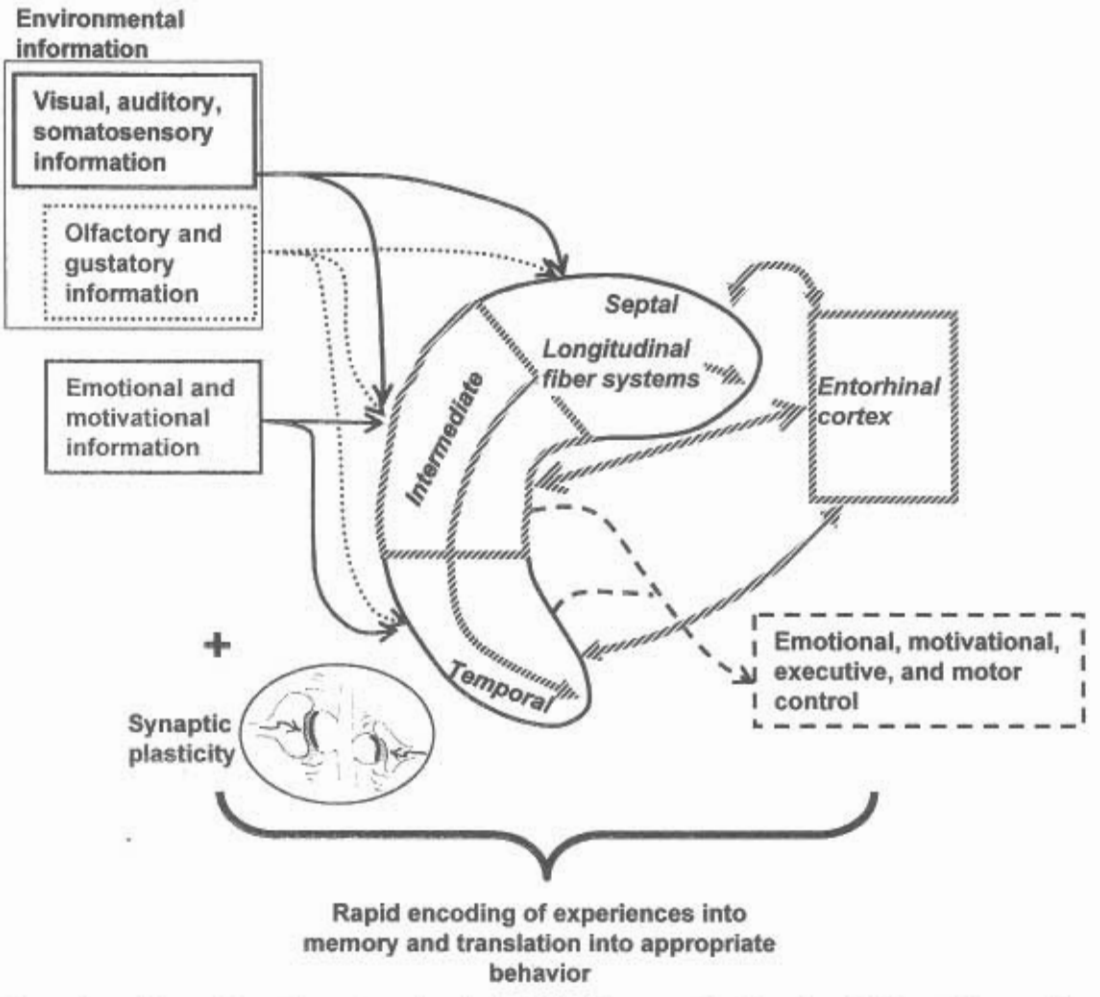

Fig. 9: From the rapid encoding of experience to adaptive behavior: a model of functional differentiation and integration along the septo-temporal axis of the hippocampus. (1) Environmental information arrives, with the exception of olfactory and gustatory information, mainly in the septal to intermediate hippocampus and is rapidly encoded into memory representations via mechanisms of synaptic plasticity; it can subsequently be retrieved via transmission through the modified hippocampal synapses. (2) Via connections of the temporal and intermediate hippocampus to the prefrontal cortex and subcortical sites, such representations can be related to emotional, motivational, executive, and sensorimotor processes. (3) Possible anatomical substrates for a septo-temporal functional integration (hatched) include: a partial overlap of the different hippocampal inputs and outputs, especially in the intermediate hippocampus; longitudinal intrahipocampal fiber systems; reciprocal connections with the entorhinal cortex.

between the anatomical connections linking the hippocampus to distinct types of information and functions /5,235,280/. In particular, the intermediate hippocampus is characterized by such an overlap of different efferents and afferents, combining a proportion of virtually all types of hippocampal connections. Second, different parts along the septo-temporal axis of the hippocampus are anatomically interconnected by longitudinal intrahippocampal fibers /5, 7,38-40,119,150,234,280/; there is also some direct electrophysiological evidence for these fibers mediating functional interactions along the septo-temporal axis of the hippocampus /16,110,194,235,236/ (but see /9,287/). Third, the entorhinal cortex may mediate interactions

between different septo-temporal levels of the hippocampus as it projects to and, in turn, receives input from the whole septo-temporal extent of the hippocampus /281/. Fourth, synchronous oscillatory activity has been suggested as a neurophysiological mechanism facilitating the cross-talk between distributed groups of neurons /50,75,96,222,265/. Interestingly, synchronous neuronal oscillations occur along the hippocampal longitudinal axis /34, 41,46,90,285/ and may hence play a role in septo-temporal integration. The substrates of these oscillations appear to involve intrahippocampal mechanisms and extrahippocampal substrates, such as the medial septum and the entorhinal cortex /32,34,46,47,59,90,148,211, 268,285/.

This model combines the ideas that the hippocampus is critical for certain types of rapid learning, but is also associated with multiple other functional domains; parts of the hippocampus distributed along its septo-temporal axis may make complementary contributions to adaptive behavior, implying an important role for interactions between different septo-temporal levels of the hippocampus. These ideas resonate with previous suggestions. As has already been pointed out (Section 1), different perspectives have associated the hippocampus with learning and memory, especially the rapid encoding of information (Section 2), but also with emotional, motivational, executive, and sensorimotor functions. Furthermore, some previous models explicitly suggested that the hippocampus may actually bridge the gap between these diverse functional domains. For example, it was proposed that, in addition to mediating aspects of place representation, the hippocampus is linked via the prefrontal cortex and subcortical sites to complementary functions, including goal representation and action selection, enabling the hippocampus-dependent place representations to be translated into appropriate spatially-oriented behavior /140,206,213, 232/. Moreover, a septo-temporal differentiation within the hippocampus is now widely accepted /5, 13,18,179,188,199,216,235,250,279,280/, and we and others have previously put forward ideas concerning complementary contributions of septal and temporal hippocampus to context fear conditioning /21,275/. In line with the present model, such behavior was suggested to rely on the septal hippocampus mainly for the rapid encoding and subsequent retrieval of a context representation, and on the temporal hippocampus to combine these representations with emotional information and to generate appropriate fear responses. Also, the importance of transmission along the septo-temporal hippocampal axis has recently been emphasized, even though mainly with respect to the association of distributed sensory inputs /235,236/.

4.1. Further development of the model

The suggested model can be tested and specified by combining pharmacological and lesion manipulations of the distinct components of the hippocampal circuitry with behavioral tests, as well as with anatomical and physiological investigations. According to the model, the septal hippocampus should mainly be important for the rapid, but not incremental, encoding of allocentric place representations based on visuo-spatial information, while the temporal hippocampus relates such representations to circuits involved in the coordination and execution of adaptive behavior. Thus, partial hippocampal lesions sparing only isolated chunks of tissue in the septal or temporal hippocampus should both disrupt behavior based on rapid place learning, while even rats with complete hippocampal lesions might show largely appropriate behavior based on place information if they can acquire this information slowly and incrementally over many repeated trials. These predictions are supported by the preliminary results of experiments from our laboratory /19/. Interestingly, the model further predicts that neurons in an isolated chunk of septal tissue, while not capable of supporting behavior based on rapid place learning without the temporal hippocampus, will still show strong place-related firing, which could be revealed by single-unit recordings. A 'functional-neuroanatomy' approach, combining lesions and behavioral tests with tract-tracing techniques, could be used to corroborate that, whether or not a chunk of hippocampal tissue can support behavior based on rapid place learning, is related to it combining sufficient sensory inputs from the dorso-lateral entorhinal cortex with sufficient connections to the

prefrontal cortex and subcortical sites. Furthermore, while selective blockade of synaptic plasticity restricted to the septal hippocampus, for example by local microinfusion of NMDA receptor antagonists, impairs behavior on rapid place learning tasks /17,144,243/, presumably by preventing the rapid encoding of place representations, blockade of synaptic plasticity restricted to the temporal hippocampus may not affect such behavior. In contrast, flavor-place paired-associate learning tasks /64,126/ may require plasticity along the septo-temporal axis of the hippocampus, so that gustatory information, a substantial part of which enters the hippocampus in its temporal part, and visuo-spatial information can rapidly be encoded into unified representations. It should, however, be noted that even place learning tasks may involve memory representations combining place with emotional and motivational information and, thus, may depend on plasticity along the septo-temporal extent of the hippocampus, as has been indicated for context fear conditioning /21,289/.

The model suggests several anatomical substrates to mediate functional integration along the septo-temporal axis of the hippocampus. One interesting possibility is that the intermediate hippocampus, combining all types of hippocampal connections, plays a key role in supporting efficient behavior on rapid place learning tasks. Furthermore, electrophysiological studies should corroborate that longitudinal intra-hippocampal fibers may mediate septo-temporal information transfer, as present evidence for this hypothesis is limited /16,110,194,235,236/ (compare /9,287/). Recently introduced micro-knife techniques to cut these fibers /161,244/ could be used to investigate their behavioral significance. For example, transection of longitudinal intrahippocampal fibers connecting septal and temporal hippocampus may disrupt behavior on rapid place learning tasks. As to clarifying the neurophysiological mechanisms or correlates of septo-temporal integration, an intriguing albeit very demanding experimental approach might involve multielectrode-array recordings of single units and field potentials along the septo-temporal axis /34,41,48,104,285/ while rats engage in behavior that involves the rapid encoding and subsequent use of place memory. Such recordings may reveal septo-temporally distributed groups of neurons with place, emotional, motivational (compare /252/), or sensorimotor correlates whose firing is linked via synchronous oscillations.

4.2. Clinical implications

The suggested perspective on hippocampal function, considering hippocampal substrates of memory processes as well as the association of the hippocampus with other behavioral processes, may help in understanding the pathophysiology of the diverse behavioral impairments in clinical populations with hippocampal dysfunctions. Thus, the proposed model of the hippocampus might account for the striking deficits in many aspects of declarative memory /58,229,240,266/ and the aberrant emotional and motivational processing /88,108/ in patients with permanent hippocampal damage, such as H.M. Furthermore, the model suggests that aberrant hippocampal morphology and physiology characterizing many neuropsychiatric populations, especially patients with schizophrenia /25,106,109,271/, may not only contribute to the subtle impairments in subtypes of declarative memory /103,164,185,189,221,256/, but also to the abnormalities in emotional, motivational, and sensorimotor functions /92,203/.

5. SUMMARY AND CONCLUSION

The present article argues that the hippocampus enables adaptive behavior based on information encoded during single or a few experiences by integrating specific representational functions, which mediate the rapid encoding and subsequent retrieval of environmental stimuli and their relations (Section 2), with links to behavioral functions necessary for the coordination and executive control of behavior (Section 3). The association with the sensory, especially the visuo-spatial, information processing critical for the representational functions of the hippocampus declines toward the temporal pole of the hippocampus (Section 2.3), while links to emotional, motivational, executive, and sensorimotor functions decline toward the septal pole (Section 3.1-3.4). A model of functional differentiation and integration

along the septo-temporal axis of the hippocampus is suggested (Section 4). It is hoped the proposed theoretical perspective will be useful in guiding future research on the hippocampal contributions to adaptive behavior, and some exemplar experiments are suggested (Section 4.1). Last but not least, possible clinical implications of the suggested model were hinted at briefly (Section 4.2).

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