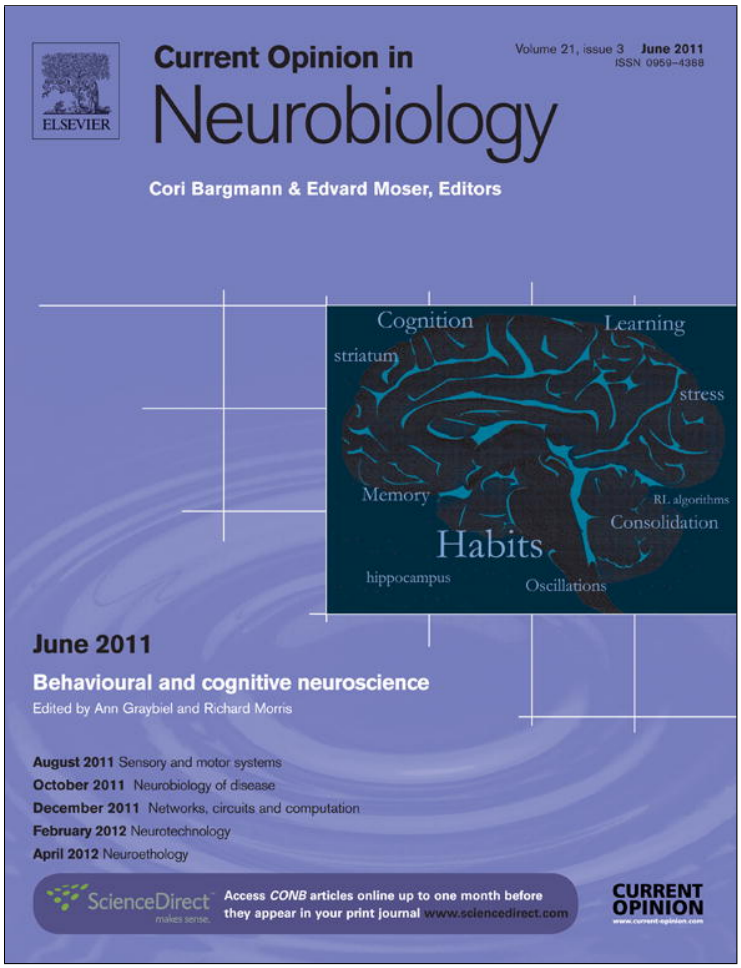

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The hippocampal learning-behavior translation and the functional significance of hippocampal dysfunction in schizophrenia

Tobias Bast

How is hippocampal learning, including place learning, translated into behavior? The hippocampus integrates, along its septotemporal axis, substrates of rapid place learning, including entorhinal–hippocampal connectivity, with functional connectivity to subcortical sites and prefrontal cortex, which play central roles in behavioral-control functions, including sensorimotor, emotional, motivational, attentional, and executive functions. I present recent evidence that such integration, for which the intermediate hippocampus is a key neuroanatomical substrate, enables translation of rapid place learning into adaptive behavior. What are the clinical implications of the hippocampal learning-behavior translation? Focusing on hippocampal overactivity, which has emerged as a central feature of schizophrenia pathophysiology, I highlight how, due to functional connectivity enabling the learning-behavior translation, hippocampal dysfunction may cause not only memory deficits, but also neural-network disruptions underlying psychosis and attentional and executive deficits.

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Introduction

The importance of the hippocampus for certain types of rapid learning, including place learning and the acquisition of episodic memory, is now firmly established [1•]. Moreover, especially the study of place learning and of place-related neuronal activity has revealed key aspects of the neuroanatomical connectivity and the neurophysiological and neurocomputational mechanisms underlying hippocampal encoding, storage, and retrieval of memory [1•,2–5]. However, as learning theorists have long emphasized, 'learning', that is, acquisition and storage of information, and 'performance', that is, use of such information for appropriate behavior on a task, are conceptually distinct [6,7], raising the question: How is hippocampus-mediated learning translated into behavior?

This paper has two main objectives: First, I highlight a key feature of the hippocampus (referring to the cytoarchitectonic subfields dentate gyrus, CA1-3, and subiculum): the hippocampus integrates along its longitudinal, that is, septotemporal, axis i) the neuronal substrates of certain types of rapid learning, including place learning, with ii) links to diverse behavioral-control functions, including sensorimotor, emotional, motivational, attentional, and executive functions; this integration, for which the intermediate hippocampus is an important neuroanatomical substrate, enables the translation of rapid place learning into adaptive behavior. Second, focusing on hippocampal overactivity in schizophrenia, I show that an 'integrative' perspective, considering not only hippocampal mechanisms of learning, but also links to behavioral control, leads to new hypotheses concerning the functional significance of hippocampal dysfunction in neuropsychiatric diseases.

From rapid place learning to adaptive behavior along the septotemporal axis of the hippocampus

Over recent years, neuroanatomical, neurophysiological, and neurocomputational evidence has converged to suggest that interactions with the entorhinal cortex are crucial for the visuo-spatial information processing underlying hippocampal rapid place learning, as reflected by formation of place codes, that is, place-related firing of principal neurons, in the hippocampus [1•,3,5,8]. The translation of hippocampal place learning into adaptive behavior must involve behavioral-control functions, such as sensorimotor, motivational, emotional, attentional, and executive processes. The hippocampus has strong neuroanatomical and functional connectivity with brain systems playing central roles in such behavioral-control functions, including prefrontal cortex, mediodorsal and ventral striatum, amygdala, hypothalamus, and the dopamine projections from the ventral tegmental area (VTA) to the forebrain; it is both plausible and supported by experimental evidence (also see below) that such functional connectivity is important for the hippocampal learning-behavior translation [9•,10•,11••,12••,13–17]. Only when information encoded by the hippocampus does not change after learning and could be consolidated into the neocortex [18–20], so that neocortical links to behavioral control [17] may mediate translation into behavior, the direct hippocampal learning-behavior

translation may be circumvented.[1] The suggestion that hippocampal interactions with medial prefrontal cortex, mediodorsal striatum, and nucleus accumbens are important for performance based on rapid place learning is supported by studies that combined behavioral testing with multi-site electrophysiological recordings or disconnection approaches. Multi-site recordings in rats and mice revealed that direct interaction and coordination of neuronal activity in the hippocampus with activity in medial prefrontal cortex [24•,28–30], mediodorsal striatum [31] and nucleus accumbens [32] correlates with the accurate use of rapidly learnt place information during foraging behavior. Moreover, studies using crossed unilateral lesions or pharmacological manipulations of the relevant brain sites showed that disconnection of the hippocampus from the medial prefrontal cortex [33–37], from prefrontal dopamine transmission [38], from the mediodorsal striatum [39], or from the nucleus accumbens [33,40,41] impairs rats' performance on different tasks requiring rapid place learning. If other subcortical sites, such as amygdala and hypothalamus, which have been implicated in behavioral control and have strong connectivity to the hippocampus [16], interact with the hippocampus in translating place learning into behavior remains to be examined.

Functional–anatomical gradients along the septotemporal axis of the hippocampus

An important point relevant to the hippocampal learning-behavior translation is that functional–anatomical gradients exist along the septotemporal axis, which runs from the septal pole, close to the septum, to the temporal pole, close to the amygdala.[2] Many neuroanatomical connections of the hippocampus show septotemporal topographical gradients, that is, they get weaker toward the septal or temporal pole, so that they are largely restricted to one to two thirds of the septotemporal axis. This gives rise to three partly overlapping hippocampal regions with different sets of connectivity: a septal and temporal region and between them an intermediate region [1•,11••,12••,16,42,43].[3] A corresponding septotemporal differentiation of hippocampal gene expression, recently revealed by molecular–biological studies, could underlie the development of these three regions' different connectivity patterns [45••,46••].

Concerning hippocampal place learning, it is important that the septal and intermediate, but not the temporal, hippocampus are strongly connected to the dorsolateral band of the entorhinal cortex, which receives strong neocortical visuo-spatial inputs and where neuronal firing patterns contain fine-grained spatial information; consistently, principal neurons in the septal and intermediate, but not the temporal, hippocampus show accurate place encoding [3,47•,48•]. Several other recent findings support that hippocampal contributions to place learning and memory decline from the septal toward the temporal pole: situations with high place-memory demand increased metabolic activity in the septal, but not the temporal, hippocampus [49•]; incidental, that is, non-reinforced, visuo-spatial learning triggered molecular plasticity mechanisms in the septal, but not the temporal, hippocampus [50•]; and *in vitro* electrophysiological experiments revealed that the septal and intermediate hippocampus show a higher capacity for the induction of long-term potentiation (LTP; a form of synaptic plasticity that has long been linked to place learning [1•,4,11••]) than the temporal hippocampus [51]. Moreover, under some conditions, rats with partial hippocampal lesions sparing only the septal hippocampus can show good performance on place-memory tests, whereas rats with similarly sized hippocampal lesions sparing only the temporal pole cannot [52,53]. The exact conditions enabling a residual septal hippocampal pole to sustain performance on place-memory tests remain to be clarified. However, as discussed in [12••], it seems to be important that relevant place information is stable during training, allowing for consolidation into the neocortex, so that the direct hippocampal learning-behavior translation may be circumvented during testing. By contrast, in situations requiring the rapid learning of frequently changing place information, partial hippocampal lesions impair task performance even if the septal hippocampus is spared. In such situations, place memory cannot be consolidated into the neocortex, so that performance is likely to depend on direct hippocampal links to behavioral control. As outlined in the following paragraph, these links are largely featured by the temporal and intermediate, but not the septal, hippocampus.

Hippocampal links to brain systems involved in behavioral control show an opposite septotemporal gradient to the hippocampal connectivity thought to underlie place learning and memory: direct neuroanatomical connections to prefrontal cortex, nucleus accumbens, mediodorsal striatum, amygdala, and hypothalamus and the (positive) modulation of VTA dopamine projections to the forebrain are largely via the intermediate and temporal, but not the septal, region of the hippocampus

[1] However, it should be noted that, even though the consolidation of information acquired by the hippocampus may involve hippocampal interactions with entorhinal and sensory cortices [21–23], direct interactions of the hippocampus with the medial prefrontal cortex [18,24•,25,26] and ventral striatum [27] have also been implicated by recent work, especially when hippocampal memory needs to be linked to rule or motivational information.

[2] Septal and temporal are often referred to as dorsal and ventral in rodents and as posterior and anterior in primates.

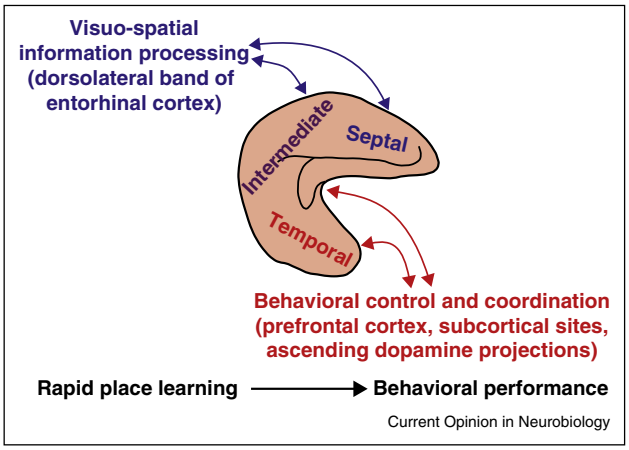
[3] Apart from septotemporal topography, hippocampal neuroanatomical connectivity is also characterized by transverse topography, that is entorhinal–hippocampal connections and many intrinsic connections between hippocampal subfields are preferentially between particular transverse locations within entorhinal cortex or hippocampal subfields (see [43] and the chapter by Amaral and Lavenex in [1•]). Interestingly, a recent place-cell study revealed a functional correlate of the transverse topography of enthorinal-CA1 connectivity [44], even though the relevance for the hippocampal learning-behavior translation is not clear.

[1•,4,11••]. Consistently, several behavioral-control functions, including sensorimotor processes, such as locomotor activity, and fear/anxiety-related processes, are more strongly modulated by experimental manipulations of the temporal to intermediate hippocampus than by comparable manipulations of the septal hippocampus [11••,53,54] and neural-activity correlates of anxiety [48•,54] and of reward-related information are more pronounced in the temporal than in the septal hippocampus [48•,49•,55•]. To summarize, whereas the septal to intermediate hippocampal regions, interacting with the dorsolateral band of the entorhinal cortex, can mediate accurate place learning, the intermediate to temporal regions provide the links to behavioral-control functions mediated by prefrontal cortex and various subcortical sites and the VTA dopamine projections (Figure 1).

Translation of rapid place learning into behavior: a key role for the intermediate hippocampus

This consideration of septotemporal functional–anatomical gradients suggests a key role of the intermediate hippocampus in behavior based on hippocampal rapid place learning: this region, where substrates of accurate place encoding converge with direct links to behavioral control (Figure 1), may be important for translating rapid place learning into appropriate behavior.

Figure 1

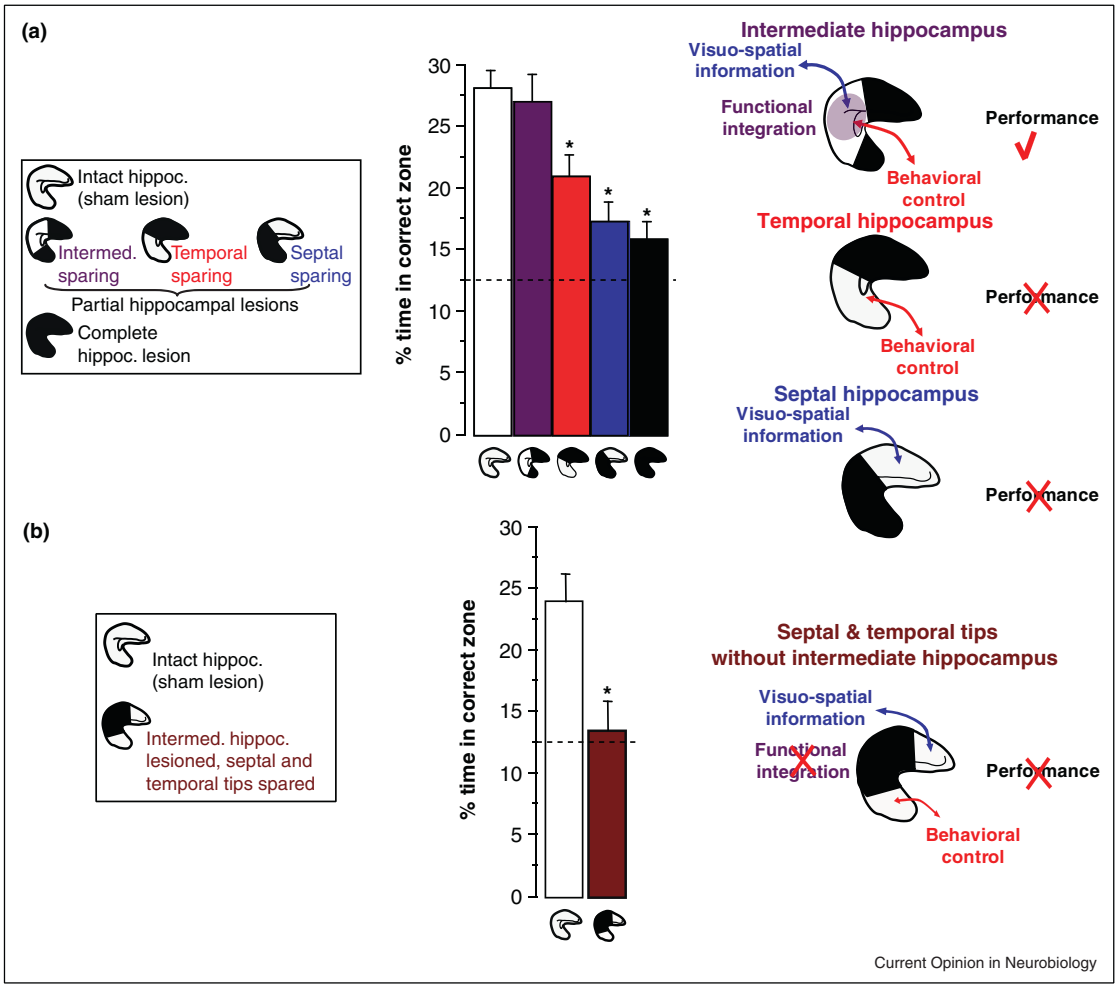


From rapid place learning to behavioral control: functional connectivity along the septotemporal axis of the hippocampus. The hippocampal functional connectivity likely to be particularly relevant for rapid place learning and its translation into adaptive behavior is differentially distributed along the septotemporal axis (running from the septal pole, close to the septum, to the temporal pole, close to the amygdala). Interactions of the septal to intermediate hippocampus with the dorsolateral band of the entorhinal cortex play a key role in the visuo-spatial processing underlying rapid accurate place learning, whereas functional links of the temporal to intermediate hippocampus to prefrontal cortex and subcortical sites, including ascending dopamine projections from the ventral tegmental area to the forebrain, provide access to behavioral-control functions, including sensorimotor, emotional, motivational, attentional, and executive functions. Note that these two sets of functional connectivity converge in the intermediate hippocampus, suggesting a key role for this region in translating rapid place learning into behavior.

We recently tested this idea in rats [12••]. First, we examined the effects of partial hippocampal lesions, which spared distinct parts along the septotemporal axis, on performance on the watermaze delayed-matching-to-place (DMTP) task. On this task, rats can rapidly learn the novel, daily changing, place of a hidden escape platform during trial 1 of each day and then use the place memory on subsequent trials of the same day to efficiently locate the platform. The DMTP task is analogous to human everyday problems, such as returning to the place where we parked our car or placed our keys on a particular day. Importantly, the relevant place information changes daily and can, therefore, not be incrementally acquired or consolidated into neocortex [18–20,56] (whereby the direct hippocampal learning-behavior translation could be circumvented). Our experiments revealed that the intermediate hippocampus, but not the septal or temporal pole, can largely sustain behavioral performance on the DMTP task without the rest of the hippocampus and is necessary for task performance. This is consistent with the idea that the intermediate, but not the septal or temporal, hippocampus provides the neuroanatomical integration of substrates of rapid accurate place encoding with direct links to behavioral control; thereby, the intermediate hippocampus enables not only the relevant place learning, but also its translation into behavioral performance[4] (Figure 2). Second, we corroborated that the intermediate hippocampus makes a unique contribution to the translation of rapid place learning into behavior, rather than to rapid place encoding per se. Using *in vivo* electrophysiological models of hippocampal learning, including LTP and place-related neuronal firing (to study hippocampal information encoding independently of behavioral performance), we demonstrated that a residual hippocampal circuitry at the septal pole, without the rest of the hippocampus, can sustain normal long-term plasticity and, most importantly, rapid place encoding (Figure 3), even though, without the intermediate hippocampus, such a hippocampal remnant cannot mediate the hippocampal learning-behavior translation and, therefore, cannot sustain task performance based on such place learning (see Figure 2a, bar graph, blue bar).

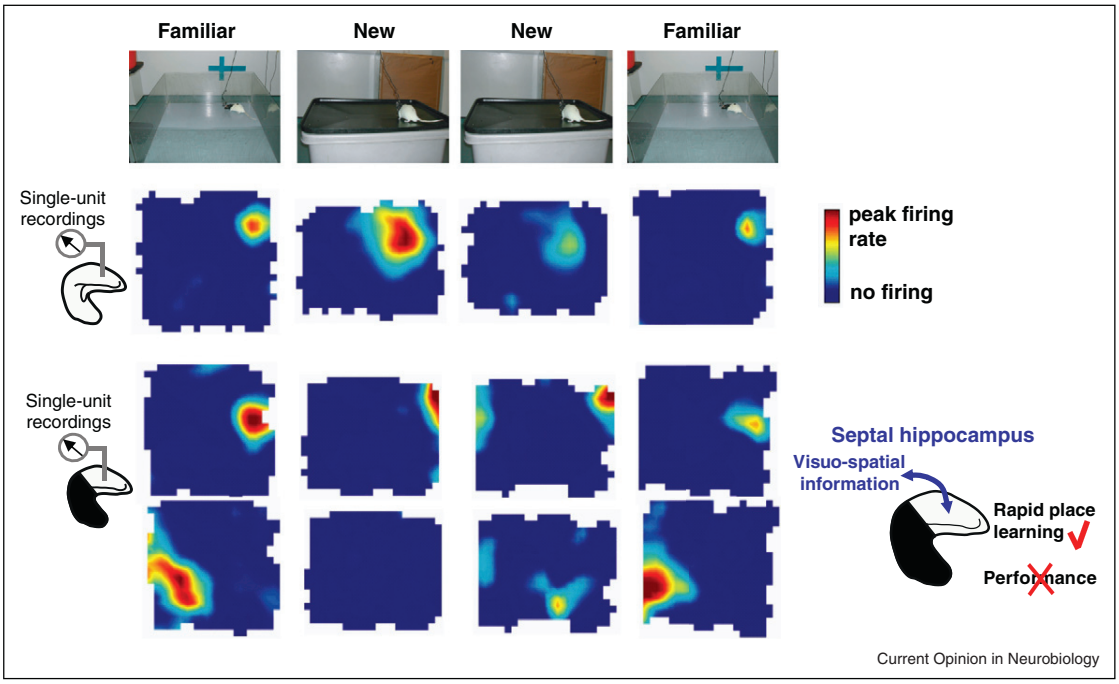
[4] Alternatively, intact navigation in rats with hippocampal residuals in the intermediate region may reflect that this region, apart from mediating accurate place representations similar to the septal pole, also contains neurons with larger-scale place fields that have been hypothesized to aid route planning [3]. However, if this was the key role of the intermediate hippocampus, rats with hippocampal residuals at the septal pole should show a selective deficit in route finding, that is increased latencies or path lengths to reach the platform, whereas search preference for the target area should be relatively normal once the rats have reached it. Such a selective route-finding deficit was not supported by our behavioral data [12••].

Figure 2



Behavioral performance based on rapid place learning: a key role for the intermediate hippocampus [12••]. Rats were trained on the delayed-matching-to-place (DMTP) watermaze task, on which they can rapidly learn the novel, daily changing location of a hidden escape platform during trial 1 of each day and then use the place memory for efficient navigation on trial 2 and subsequent trials. Following pretraining on this task, rats received partial ibotenate-induced hippocampal lesions sparing approximately 40% of hippocampal volume in distinct septotemporal regions to examine their contributions to task performance. Sham-operated rats with an intact hippocampus and rats with complete hippocampal lesions were included as comparison groups. In the hippocampus drawings used to indicate the different lesion groups, white represents spared intact tissue, and black indicates lesioned tissue. The bar graphs show the main performance measure: search preference on trial 2 for the correct zone, that is, the zone containing the platform location. To measure search preference, trial 2 was run as probe, with the platform out of the rat's reach for the trial's first 60 s. The total time spent in eight symmetrically arranged and non-overlapping zones, including the correct zone, was measured, and search preference was expressed as percentage of time spent in the correct zone (% time in correct zone); chance level was 12.5%, which is indicated by the stippled lines in the bar graphs. Performance was tested with retention delays of 15–30 s or 20 min between trial 1 and 2. However, lesion effects were independent of retention delay, and data were collapsed across the two delays. An asterisk (*) in the bar graphs indicates a significant difference from the sham-operated group. **(a)** Partial lesions sparing the intermediate hippocampus left task performance intact, whereas partial hippocampal lesions sparing temporal or septal pole strongly impaired performance (bar graph adapted from Figure 2D in [12••]). These findings can be accounted for as indicated in the cartoons on the right: the intermediate hippocampus integrates the two sets of functional connectivity required for rapid place learning and its translation into performance (compare Figure 1), whereas temporal and septal hippocampus only feature one of the two complementary sets of functional connectivity. **(b)** Is the intrahippocampal integration of links to visuo-spatial processing and to behavioral control in the intermediate hippocampus necessary for task performance based on rapid place learning, or could these two functional links make independent, parallel contributions? To decide between these alternatives, rats with partial hippocampal lesions that removed the intermediate hippocampus, but spared the septal and temporal tip (20% of hippocampal volume spared at each tip) were tested. Such lesions completely abolished task performance (bar graph from Figure 6C in [12••]). As indicated in the cartoon, this corroborates that independent parallel contributions of hippocampal links to visuo-spatial information processing and to behavioral control are not sufficient to sustain behavioral performance based on rapid place learning, but that integration of these links in the intermediate hippocampus is required.

Figure 3



A residual hippocampal circuitry at the septal pole can sustain rapid place encoding: remapping of place-related neuron firing [12••]. Single-unit firing was recorded from the CA1 region of the septal hippocampus during a series of four trials in a familiar and a new environment. Firing-rate maps during these trials are shown for one neuron recorded from a rat with an intact hippocampus (top row of rate maps; from Supplementary Figure S6 in [12••]) and for two neurons recorded from a rat with a partial lesion sparing ca. 40% of hippocampal tissue at the septal pole (two bottom rows; from Figure 5C in [12••]). Neurons from an intact hippocampus and from a residual circuitry at the septal pole both showed stable and accurate place codes in the familiar environment and, importantly, stable remapping of place-related firing in the new environment, demonstrating rapid encoding of new place information (note that one of the neurons recorded from the septal hippocampal residual formed a new place field in the new environment, whereas the other one virtually ceased firing). As indicated by the cartoon, these findings support that a residual hippocampal circuitry at the septal pole can sustain rapid place encoding due to links to visuo-spatial information processing, even though, without the intermediate hippocampus, the place codes cannot be translated into behavioral performance (compare Figure 2a, bar graph, blue bar).

The summarized data strongly support the model sketched in Figure 1 and point to the intermediate hippocampus, where neural substrates of rapid accurate place learning converge with links to behavioral control, as the neuroanatomical basis for the translation of rapid place learning into behavior. This raises three main questions for future research:

- Which interactions of the intermediate hippocampus with prefrontal and subcortical sites mediate the place learning-behavior translation? For example, combining disconnection approaches with testing on the watermaze DMTP task, it remains to be specified which functional connectivity underlies the key role of the intermediate hippocampus on this task. Consistent with the possibility that interactions with medial prefrontal cortex and mediodorsal striatum are important, there is evidence that these sites contribute to task performance [57]; however, the conditions under which this is the case (e.g. [58]) and whether it reflects interactions with the hippocampus, or independent parallel contributions, remain to be clarified.
- What neuronal wiring and which neurophysiological mechanisms within the intermediate hippocampus mediate the place learning-behavior translation? More specifically, do the relevant functional links (i.e. to accurate visuo-spatial processing and to behavioral control) converge on one septotemporal level, or even on single neurons, within the intermediate hippocampus; or are longitudinal intrahippocampal fibers (which span the whole extent of the intermediate hippocampus [42]) and coordinated neuronal activity along the septotemporal axis (presumably mediated by these longitudinal fibers) [48•,59,60] important in integrating the different functional links?
- Does the crucial role of the intermediate hippocampus extend to other situations involving behavior based on rapid visuo-spatial learning, such as appetetive and aversive context or place conditioning?

Implications for the functional significance of hippocampal dysfunction in schizophrenia

Compelling clinical evidence has accumulated for altered hippocampal function in schizophrenia [61–64]. Hallmark symptoms of schizophrenia include psychosis (hallucinations, delusions) and neurocognitive deficits, comprising memory, attentional, and executive deficits. Neurocognitive deficits have come to the fore, as they contribute strongly to patients' functional disability and are largely resistant to current antipsychotic treatments, persisting even in the absence of psychosis [65]. To which symptoms does hippocampal dysfunction contribute and, if so, how?

There is good evidence for disrupted hippocampal memory mechanisms in schizophrenia, and attempts to account for the functional significance of hippocampal dysfunction in schizophrenia often center on aberrant memory mechanisms [62–64,66–68]. Focusing on hippocampal overactivity in schizophrenia, which has emerged as key feature of schizophrenia pathophysiology (see next paragraph), I will highlight how consideration of the hippocampal functional–anatomical organization outlined in the first part of the paper leads to new mechanistic hypotheses concerning the contribution of hippocampal dysfunction to schizophrenia symptoms. To avoid misunderstanding, it is important to note that hippocampal overactivity, that is, tonically elevated activity, does not imply a gain of normal hippocampal function (which requires appropriate temporal regulation of hippocampal activation), but rather interference with normal processing within hippocampus (somewhat similar to a lesion) and aberrant drive of hippocampal projections (different from a lesion), interfering with normal processing in efferent sites. The proposed functional–anatomical model (Figure 1), addressing the hippocampal learning-behavior translation and considering hippocampal links to behavioral control, offered a suitable conceptual framework to understand the data of our recent lesion study ([12••], Figure 2), which would have been difficult to explain by solely considering hippocampal mechanisms of learning and memory. Similarly, this model, especially the consideration of hippocampal links to behavioral control, offers a new understanding of how aberrant hippocampal function in schizophrenia may contribute to symptom generation, beyond interference with memory mechanisms.

Hippocampal overactivity in schizophrenia

Following initial reports in the early nineties [69], functional-imaging studies have consistently found metabolic hippocampal overactivity in schizophrenia patients under resting conditions, whereas memory task-related hippocampal recruitment may often be impaired [62–64]. Recently, functional-imaging data have converged with neuropathological and genetic findings and with evidence from animal models to point to hippocampal overactivity due to disinhibition (i.e. reduced GABAergic inhibition) of hippocampal neuronal firing as a central feature of schizophrenia pathophysiology[5] [70••]. Concerning symptoms, hippocampal overactivity has been related to deficits on tasks requiring episodic memory (i.e. the memory of unique events, such as where we parked our car or placed our keys on a specific occasion) and to psychosis [62,63,70••]. Recently, Schobel *et al.* [71••] reported that hippocampal overactivity, as indicated by increased cerebral blood volume, predicts progression from a prodromal state to schizophrenia and correlates with psychotic symptoms. However, it remains to be clarified if hippocampal overactivity really causes impairments on memory tasks and psychotic symptoms, and by what mechanisms. Moreover, hippocampal functional connectivity (Figure 1) suggests that hippocampal overactivity may also cause deficits in executive and attentional functions (see below).

Functional significance of hippocampal overactivity: new hypotheses

The functional–anatomical model sketched in Figure 1 suggests that, depending on the septotemporal level, hippocampal overactivity may disrupt different neural networks and contribute to a wide range of deficits characterizing schizophrenia:

- Pronounced overactivity involving the temporal to intermediate hippocampus may strongly drive projections to prefrontal cortex and subcortical sites, and VTA dopamine projections to these areas. Two main effects of this may be extensive psychosis-related behavioral disruptions, which have long been linked to striatal dopamine hyperfunction [72], and a disruption of fronto-striatal attentional and executive mechanisms [73–76], which characterizes schizophrenia [77,78]. This hypothesis resonates with proposals that hippocampal overactivity plays a key role in the generation of an overactive dopamine system and of psychosis [70••,79,80••,81••] and that hippocampal dysfunction in schizophrenia may partly manifest through interaction with the prefrontal cortex [82–84].
- Overactivity involving the temporal to intermediate hippocampus may also interfere with memory tasks by disrupting the normal hippocampal learning-behavior translation [12••].
- If hippocampal overactivity is restricted to the septal hippocampus, this may not cause psychosis-related effects or attentional and executive deficits (even though it may interfere with normal memory processing

[5] At first glance, hippocampal overactivity may appear inconsistent with hippocampal volume reduction, a well-established brain pathological feature of schizophrenia [61–64]. However, hippocampal overactivity appears to precede, and may actually cause, hippocampal volume reduction, even though the underlying mechanisms remain to be revealed [62,63,70,71••].

by disrupting relevant interactions between septal hippocampus and parts of the entorhinal cortex [3]).

Overall, according to these hypotheses, overactivity of the hippocampus (especially of temporal to intermediate regions) may underlie psychosis and key neurocognitive deficits (i.e. memory and attentional/executive deficits) in schizophrenia. Intriguingly, in the study by Schobel *et al.* [71••], overactivity in the anterior (i.e. temporal to intermediate) hippocampus predicted psychotic symptoms, providing correlational support for aspects of the first hypothesis, even though causality and underlying mechanisms remain to be clarified.

Testing the hypotheses in animal models of hippocampal overactivity

Animal models offer a unique opportunity to study if and how hippocampal overactivity contributes to schizophrenia-related symptoms. Evidence from a neuro-developmental rat model of schizophrenia suggests that overactivity of the temporal to intermediate hippocampus, as reflected by a higher firing rate of neurons in this region, mediates dopamine-dependent psychosis-related behavioral changes (enhanced locomotor response to amphetamine) [81••]. Furthermore, studies using local microinfusions of excitatory drugs, such as NMDA, or of disinhibitory drugs, such as the GABA-A antagonist picrotoxin, to induce hippocampal overactivity at different septotemporal levels in rats support that overactivity of the temporal to intermediate hippocampus can cause psychosis-related sensorimotor effects (including locomotor hyperactivity and disruption of prepulse inhibition), even though the underlying interactions with hippocampal projection sites largely remain to be determined [54].

The hypothesized contributions of hippocampal overactivity to key neurocognitive deficits, that is, deficits on memory tasks and in attention and executive function, have not yet been tested. Importantly, excellent preclinical behavioral tests exist to address these issues in rat models: For example, the watermaze DMTP test [12••], which was described above, resembles the everyday memory task of using newly learned places and routes, with which schizophrenia patients have marked difficulties [85], whereas the rodent 5-choice-serial-reaction-time test resembles continuous-performance tests used to reveal attentional and executive deficits in schizophrenia patients and is highly sensitive to interference with fronto-striatal networks [73–75].

Conclusions

To understand the contributions of normal hippocampal function to adaptive behavior and of hippocampal dysfunction to neuropsychiatric symptoms, we must consider learning and memory mechanisms, including entorhinal–hippocampal interactions playing a key role in rapid visuo-spatial learning, as well as hippocampal–prefrontal/subcortical links providing access to behavioral-control functions. First, the integration of these complementary functional substrates, for which the intermediate hippocampus is important, enables the translation of rapid place learning into adaptive behavior. Second, owing to these diverse functional links, hippocampal dysfunction, such as hippocampal overactivity in schizophrenia, may cause neural-network disruptions resulting in a wide range of functional impairments, including difficulties with everyday memory tasks, but also psychosis and attentional and executive deficits.

Future research is necessary to characterize further the neuroanatomical and neurophysiological properties of the intermediate hippocampus that underlie the hippocampal learning-behavior translation, and to specify the crucial hippocampal–prefrontal/subcortical interactions. Furthermore, the hypothesized contributions of hippocampal overactivity to schizophrenia-related behavioral and cognitive deficits largely remain to be tested.

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- • of special interest
- •• of outstanding interest

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