BOOK REVIEW

The hitchhiker's guide to *The Hippocampus*

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The Hippocampus (Vols. 3 and 4)

Edited by Robert L. Isaacson and Karl H. Pribram.
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The goal of the four volumes of *The Hippocampus*, edited by Isaacson and Pribram, was to bring together in one place the important information about hippocampal anatomy, physiology, and functions. In Volumes 3 and 4, which were recently published, Isaacson and Pribram have attempted to include "the exciting discoveries that have occurred since 1975." It is clear to me that the past 12 years have provided hippocampal investigators with the opportunity to live through interesting times, although this will not necessarily be obvious to readers of these two volumes.

During these 12 years, important progress in the understanding of the hippocampal formation was made at several levels: (1) connectivity, (2) single-unit recording in freely behaving animals (rodents and primates), (3) pharmacology, (4) long-term changes in synaptic efficacy, and (5) analysis of memory defects in monkeys and humans with hippocampal damage. I will outline some of these important discoveries below, but before I do so it is probably worthwhile to provide a somewhat broader background within which this hippocampal work is being conducted. It has only been during the past approximately 15 years that there has been a rapid increase in our information about the hippocampus. This has been driven in large part by the novel application of techniques from biochemistry, electrophysiology, neuroanatomical tracing, behavioral testing, and, to a lesser extent, mathematics. The examples set in other areas of science suggest, however, that a significant change in our understanding of the hippocampus or, more generally, the cerebral cortex, will probably be brought about only after enough new information, derived from a multitude of new techniques or methods of observation, is accumulated to generate general dissatisfaction with the theoretical concepts inherited from an earlier generation. Although there

may now be isolated pockets of discontent, these two volumes provide convincing evidence that it is still business as usual in the hippocampus.

1. The most exciting new findings on connectivity have been concerned with the previously unappreciated extent of hippocampal output to the cortex. Swanson has convincingly presented the case that the hippocampal formation, which receives its inputs from polymodal areas of association cortex, should be thought of as belonging to a class of "supramodal" cortex. On the basis of information from the application of recently developed techniques for tracing connections, we can now recognize that these same areas of polymodal inputs to the hippocampal formation are themselves targets for the widespread cortical output of the hippocampal formation. An understanding of the significance of these hippocampocortical connections will be a key prerequisite to the elaboration of a sensible theory of hippocampal contributions to cognition.

To some extent, as well, the interval since publication of the first two volumes of *The Hippocampus* has been characterized by a reduction in the anatomical salience attached to the traditional trisynaptic route and the lamellar organization of the hippocampus. This change in emphasis is due to several recently described findings—namely, that only a small minority of synapses within the hippocampus can be ascribed to the "trisynaptic" path, that a large number of "nontraditional" cell types have been described in some detail, that there is almost certainly a high degree of convergence/divergence in intrahippocampal connectivity, and that there is a significant degree of "cascade" of projections, forward and backward, found as one moves from the input levels (neocortical projections) to the output levels (subicular projections) of the hippocampal system.

2. Over the past few years, fundamental, new information about the hippocampus has been obtained at the single-unit level, particularly from recordings in freely moving preparations. In the "spatial" domain, work done in several laboratories by, among others, O'Keefe, Kubie, Muller, Ranck, Best, McNaughton, and Barnes, has characterized hippocampal place unit activity in well-controlled environments in response to several kinds of manipulations of local and distal cues and of behavior.

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I will offer only a few examples: Ranck has discovered a new class of "spatial" cell in the postsubiculum which markedly increases its firing rate if the animal is oriented in a specific direction, apparently independently of the animal's position or behavior. There is a "tighter" relationship between place cell firing rate and spatial location if the unit activity that precedes the animal's current location by approximately 200 msec is correlated. Cells with place field characteristics have been found in the entorhinal cortex. Factors such as movement speed, directionality, hippocampal slow-wave state, and the animal's age have been shown to modulate place cell firing rate and specificity. Finally, O'Keefe has convincingly demonstrated, under carefully controlled conditions, that the place specificity of hippocampal units is determined by the currently active memorial representation of the topological relationships among familiar (but absent) distal cues. Although it is clear to nearly everyone that the "spatial story" does not provide us with the final chapter of the history of hippocampal function, it should be equally clear that it is probably not an accident that a high proportion of hippocampal cells have spatial correlates and that cognitive mapping theory correctly identifies a large proportion of the behavioral tasks for which an intact hippocampus is necessary. At the present time, at the level of single-unit analyses and neural network models, it is these spatial correlates that will continue to provide the much-needed wedge into the unique information-processing operations that the hippocampus carries out on its cortical inputs. (It is simply misguided to dismiss the attribution of spatial functions to the hippocampus, as Isaacson does in his chapter, as an idea that "first gained and then lost favor over subsequent years" [p. 128] or, as Gray and Rawlins do in their chapter, because it is difficult to imagine a "spatial" explanation of hippocampal lesion-induced deficits in DRL performance or nonspatial reversal. In the latter case, I am reminded of the cautionary remark attributed to Sun Tzu, a military strategist: "Do not worry about your beard when you are about to lose your head.")

Outside of the domain of place cells (or nictitating membrane conditioning), important contributions have been made by Best, Rolls, Eichenbaum, Halgren, Deadwyler, Olton, and their colleagues in studying nonspatial, sensory-behavioral correlates of hippocampal unit activity in rats, monkeys, and humans. The nature of the relationship between "spatial" and "nonspatial" unit correlates has, in recent years, posed an interesting conceptual problem whose solution will lie at the heart of the unique information-processing events that take place in the hippocampal formation.

3. The recent descriptions of the different properties of the quisqualate and N-methyl-D-aspartate (NMDA) glutamate receptors in CA1 will surely prove to be of considerable importance in our thinking about the hippocampus. Understanding the operation of the NMDA receptor with its voltage and magnesium dependency presently appears to hold out the possibility of explain-

ing some of the more interesting properties of long-term enhancement (LTE) of synaptic efficacy. Important and practical contributions have been recently made to the pharmacology of these receptors. Of some considerable interest has been the demonstration that specific blockade of the NMDA receptor with 2-amino-5-phosphonovalerate (APV) prevents induction of LTE without significantly disrupting normal synaptic transmission. With the recent production of NMDA receptor blockers that can be peripherally administered, these discoveries will have opened up a significant new line of pharmacological work on the nature and significance of hippocampal synaptic plasticity.

4. A key question that has emerged clearly in the past few years, one that will be of enduring importance, concerns identification of the relationship between hippocampal LTE and memory processes. LTE is still one of our best candidate models for a memory substrate. To avoid being seriously misled by what could be relatively superficial similarities between the properties of LTE and the features we would like to see in a neural model for associative learning, we must have solid, empirical demonstrations at the *behavioral* level that LTE actually plays a role in at least one form of memory. Although some investigators who have sought to link LTE with memory recently have hit some long balls, none have hit the home run. (See what doing a sabbatical in the U.S.A. does to an otherwise normal mind?) The accelerated forgetting of spatial information in aged rats was shown to be correlated with the accelerated rate of decay of "artificial" LTE in the perforant-path-dentate connection (Barnes et al.). Saturating LTE in the perforant-path-dentate connections by electrical stimulation blocks acquisition of "spatial map" learning, but does not affect spatial working memory in a familiar radial arm maze or the retention of map learning acquired well before LTE saturation (McNaughton et al.). Sharp and her colleagues have demonstrated both short- and long-term changes in synaptic transmission in the perforant-path-dentate connection in rats that have been permitted to explore new environments. Finally, Morris and his colleagues have shown that intraventricular or intrahippocampal injections of APV that block induction of LTE but spare synaptic transmission prevent acquisition of place learning in rats.

5. The remaining area in which important progress has been made involves research with primates, both human and nonhuman. It must be acknowledged that the cornerstone for a large proportion of research on the hippocampus is the observation of dramatic impairments in recent memory following bilateral damage to the medial temporal lobe in humans. In the past 10 years, a great deal of information about human temporal lobe amnesia has accumulated. In particular, we should note the contributions made by Brenda Milner and her colleagues at the Montreal Neurological Institute in their work with cortical excision patients. They have developed a scheme for quantifying the extent of hippocampal removal and, over many years, have examined correlations with degree of impairment on a wide range of tests of memory and other cognitive func-

tions. From this work, we have clear demonstrations of complementary specialization in memory function of the left and right hippocampus and some elegant demonstrations of dissociations of contributions to memory among patient groups with temporal, frontal, or parietal lobe excisions. Squire and his colleagues have contributed an important analysis of retrograde memory loss in several forms of human amnesia. Damage to medial temporal lobe structures produces a temporally limited retrograde amnesia covering a period of several months to several years prior to damage. According to their analysis, this retrograde amnesia reflects the interruption of a very gradual process of consolidation by which medial temporal lobe structures strengthen memory representations in the neocortex. In addition, Zola-Morgan, Squire, and Amaral have described a patient with long-standing anterograde amnesia who, upon careful histological analysis, exhibited damage that was largely confined to the CA1 subfield of the hippocampus.

We now have a compelling "animal model" for human temporal lobe amnesia. In large part through the efforts of Mishkin and his colleagues with monkeys, we have reason to believe that the "global" nature of human amnesia is produced only by damage to both hippocampal- and amygdala-related memory circuits. In a series of elegant neuroanatomical and behavioral studies, this group has traced neocortical, limbic, and diencephalic components of these hypothetical memory circuits. Important progress has been made in describing the ontogeny of these components and in identifying some of the dissociable contributions of these components to behavior in monkeys.

The most important thing that I have to say about the two recent volumes of *The Hippocampus* is that they do not contain reviews of any of the above-mentioned findings. Although everyone in the field undoubtedly will have his or her own unique "hit parade" for the past 12 years

of research on the hippocampus, I think that most would be surprised to learn that none of the research in the five areas that I have briefly described is included in the contributions to the two volumes edited by Isaacson and Pribram. I consider these omissions to be fatal with respect to the claim of the editors noted at the beginning of this review. To be fair, this may be a qualified fatality, since the editors do note, in more than one place, that many of the above-mentioned researchers were contacted but that, for one reason or another, they did not contribute to these volumes.

Even though the volumes fail as a summary of the important findings in hippocampal research over the past 12 years, many of the chapters are interesting, informative, and well written. It is worth noting the chapters on the regulation of excitability in hippocampal neurons (Schwartzkroin), the generation of EEG patterns (Buzsaki), a basic description of LTE (Andersen and Hvalby), hippocampal contributions to nictitating membrane conditioning (Berger, Berry, and Thompson), and the behavioral consequences of hippocampal damage at different ages in monkeys (Mahut and Moss). In addition, the chapters by Gabriel, Sparenborg, and Stolar on interactions among hippocampal formation, cingulate cortex, and thalamus during learning and that by Jarrard on behavioral effects of selective elimination of components of the hippocampal formation make particularly important contributions. All of these chapters clearly will be of continuing use to both students and researchers. In my estimation, the remainder of these two volumes has a much more limited and specialized utility.

In sum, with noteworthy exceptions, the selection of contributions to these volumes is idiosyncratic. As listed above, the absence of coverage of significant new information seriously limits the importance of these two volumes as summaries of our current understanding of the hippocampus.