MEETING REPORT

The Parahippocampal Region: Basic Science and Clinical Implications

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In recent years, it has become clear that the cortical regions adjacent to the hippocampus deserve a good deal more attention than they had traditionally been given. A recent meeting organized under the auspices of the New York Academy of Sciences by Helen Scharfman, Menno Witter, and Robert Schwarz, “The Parahippocampal Region: Basic Science and Clinical Implications,” was a welcome step in this direction.

The meeting covered a wide range of approaches, touched on a number of structures, and might even have established some consensus among workers in the field about the proper use of several oft-confused terms. It became obvious during the course of the meeting that there was considerable confusion about how best to label structures in this part of the brain. A post-meeting wrap-up discussion generated a proposal that most agreed would help, namely, that the term parahippocampal cortex be reserved just for areas TF and TH in the primate (in rodents, the likely homologue of these areas is called the postrhinal cortex), and that the term parahippocampal region be used to embrace these areas plus the entorhinal cortex, the presubiculum, the parasubiculum, and the perirhinal cortex. The logic behind this choice, outlined by Menno Witter, is that all of these areas are reciprocally connected, they are all composed of six discernible layers (in contrast to the three-layered hippocampal formation, comprising the dentate gyrus, CA fields, and subiculum), and they all project to at least some part of the hippocampal formation. It was agreed that the use of the term “region” conveys geographical proximity, and leaves the question of functional relatedness open, as it should be at this point.

The meeting, held in Baltimore from September 23–26, 1999, was divided into five major content areas, starting with neuroanatomical issues, and ending with a number of presentations on the presumed cognitive functions of structures in the parahippocampal region. Along the way it touched on, among other subjects, epilepsy, Alzheimer’s disease, recognition memory, animal models of amnesia, neurogenesis and regeneration, computational models, oscillations, neuroimaging, schizophrenia, and kindling. This range of topics gives some sense of why interest in the parahippocampal region is only seen in primates, and is particularly large in humans. This region is sparsely myelinated, predominantly

entorhinal areas project to the same cells in the dentate gyrus and CA3, but to different cells in CA1 and the subiculum. Whereas the entorhinal cortex projects to all subfields of the hippocampus along about 25% of its length, projections from perirhinal and parahippocampal cortices are restricted largely to the subiculum, ranging over less than about 10% of its length. On the return side, Witter noted that hippocampal projections to entorhinal cortex terminate in layer 3 as well as layer 5, and that the standard concept of layers 2/3 only providing input to hippocampus, and layer 5 being the only layer receiving hippocampal outputs, is therefore an oversimplification.

Using electrophysiological methods, Fernando Lopes da Silva showed that there are direct inputs from perirhinal and postrhinal areas into the hippocampus, in addition to the indirect inputs via the entorhinal cortex. The subiculum in particular appears to receive both direct and indirect afferents of this sort, although it seems likely that these two classes of input terminate in different layers. Stan Leung described the details of entorhinal and perirhinal inputs to the hippocampus based on current source density analyses.

Rebecca Burwell carried the anatomy one step further back, noting that the perirhinal area projects mostly to the lateral entorhinal cortex, whereas the postrhinal area projects mostly to the medial entorhinal cortex. The functional implications of this pattern remain to be elucidated. Burwell also pointed out the vast increase in relative size of the perirhinal area in humans, as compared to rodents and monkeys. In the mouse and rat, the entorhinal cortex is larger than the perirhinal cortex, but in monkeys this relationship is reversed, and the perirhinal cortex is about twice the size of the entorhinal cortex. In humans, this ratio increases to about six times. The parahippocampal cortex also increases somewhat in size in relation to the entorhinal cortex, but not anything like the change observed in the perirhinal cortex.

Heiko Braak focused on the entorhinal cortex, pointing out the existence of a unique transitional zone between the entorhinal cortex and temporal neocortex that is only seen in primates, and is particularly large in humans. This region is sparsely myelinated, predominantly
postnatally, which might account for a particular vulnerability in disorders such as Alzheimer’s disease (AD), Huntington’s disease, Pick’s disease, and several forms of dementia other than AD. Dysfunction in this region implies that impaired flow of information through the entorhinal cortex, and into the hippocampus proper, links all of these disorders.

Asla Pitkänen added to this picture by describing the complex connectivity between parahippocampal region structures and the amygdala. There are numerous inputs to the amygdala from the perirhinal cortex, entorhinal cortex, CA1, and the subiculum within the hippocampal formation. All these structures plus the postrhinal cortex and the parasubiculum receive inputs from the amygdala. The lateral nucleus of the amygdala projects most strongly to entorhinal, perirhinal, and postrhinal areas; the basal nucleus of the amygdala projects mainly to the subiculum and the temporal part of CA1. At a finer grain, it appears that a given neuron in the amygdala can innervate several components of the parahippocampal region.

Gyorgy Buzsáki turned his attention to the functional implications of one of these anatomical facts: that there appear to be two major inputs from the entorhinal cortex to the hippocampus. He suggested that the hippocampus takes novel inputs from layer 3 of the entorhinal cortex, reconstructs them, and feeds them back out to layer 5. Any mismatch between layers 3 and 5 is computed in layer 2 within a single gamma cycle, and then fed back into the hippocampus as an “error” signal. The hippocampus then uses this signal to form appropriately orthogonalized representations of its inputs. Angel Alonso discussed mechanisms by which entorhinal ensembles can generate the rhythmic activity demanded by models viewing the entorhinal cortex as a kind of gateway to the hippocampus. He proposed that neurons in layers 2 and 5 of the entorhinal cortex have the kind of intrinsic oscillatory properties needed to subserve a coordinating role of the type these models envision.

The idea that the hippocampus, and/or portions of the parahippocampal region, serve as comparators was repeated by a number of speakers, and indeed has a long history in the field, going back at least to the work of Vinogradov and of Sokolov. Uwe Heinemann added important information about differences between entorhinal cortex layer 2 and layer 3 inputs to the hippocampal formation. As required by Buzsáki, layer 3 cells are active before layer 2 cells; but they appear to project to different parts of the hippocampal formation. This caveat will have to be accounted for in future versions of Buzsáki’s model, and we will need a much clearer idea of what is being compared to what if we are to fully understand the notion of a comparator.

A number of speakers addressed a variety of clinical implications of parahippocampal function and dysfunction. Steve Arnold and Francine Benes considered various changes in hippocampal and parahippocampal regions associated with schizophrenia. Arnold discussed the status of hypothesized changes in the entorhinal cortex, where sporadic reports have indicated abnormalities suggestive of migrational difficulties during prenatal development. He also noted decreases in MAP-2 protein in the subiculum, which could be responsible for smaller neuron size both there, in the CA1 field of the hippocampus, and in layer 2 of the entorhinal cortex. Benes noted striking reductions in nonpyramidal cells in CA2, but no change in pyramidal cells anywhere in the hippocampus. In an animal model, downregulation of a GluR subunit seemed associated with alterations in corticosterone receptors. The possibility that stress plays some causal role in the changes associated with schizophrenia is intriguing. Eero Castren discussed the possibility that the neurochemcistry of schizophrenia resembles in some respects the effects of NMDA antagonists such as MK-801 and PCP. Monitoring immediate early gene activation after MK-801 may reveal the neuronal pathways that mediate psychotic behavior. Systemically applied MK-801 reduced expression of some NMDA receptor subunits in the entorhinal cortex, and these effects were reversed by the antipsychotic drugs clozapine and haloperidol.

Gary Van Hoesen noted that substantial damage can be seen in the parahippocampal region in preclinical AD, before any obvious signs of dementia emerge. He suggested that the perirhinal cortex may be the site of the earliest neuropathologies associated with AD. Leyla DeToledo-Morrell reported data using a new protocol to estimate the size of the entorhinal cortex from MRIs. In nondemented elderly patients, changes in entorhinal cortex and hippocampal volume were best associated with performance on learning tasks involving early or delayed recall, respectively. She further indicated that although degeneration of both the entorhinal cortex and hippocampus occurs before the onset of obvious dementia, it is entorhinal volume that best differentiates very mild AD patients from nondemented ones.

The unique susceptibility to epileptiform activity of many areas in the parahippocampal region was the focus of a number of talks. Lew Haberly and Meyer Jackson considered the endopiriform nucleus of the piriform cortex. This area, and in particular the pre-endopiriform nucleus, appears to be particularly powerful in eliciting seizures. Haberly presented a seizure model involving disinhibition in the pre-endopiriform area that slowly spread through the piriform cortex, and into the parahippocampal cortex, subiculum, and finally hippocampus. The rate of spread in the model closely matched empirical data. Jackson used fluorescence imaging to track seizures in slices of piriform cortex, showing that discharges began in the endopiriform nucleus and adjoining perirhinal cortex, but were preceded by a low-level plateau depolarization at a different site. Dan McIntyre presented data showing that the perirhinal cortex kindles faster than any other brain region, and that cortical structures play a critical role in the behavioral manifestations of the seizure.

Helen Scharfman and Robert Schwarz focused on the role of the entorhinal cortex in epilepsy, and on the consistent finding of layer 3 medial entorhinal cortex damage, both in epilepsy patients and in animal models. Scharfman pointed out that there are several parallels between layer 3 entorhinal cortex cells and the mossy cells of the dentate gyrus. Similarly, epilepsy-resistant cells in the entorhinal cortex (layer 2 pyramids) and dentate gyrus (granule cells) also share many characteristics. Schwarz noted that after layer 3 entorhinal cortex damage there is an upregulation of hippocampal NMDA receptors, a loss of inhibition, and ultimately spontaneous epileptic seizures. He also noted that removal of presubicular cells somehow protects layer 3 entorhinal cells from an excitotoxic insult. It seems quite clear that a key event is the loss of the layer 3 cells, but just why these cells are so vulnerable remains unknown.
Robert Nitsch and Thomas Deller discussed the sequellae to lesions in the entorhinal cortex. Nitsch noted that the regeneration observed in the termination zone of the perforant path involves a variety of changes in glial morphology and function, interacting with immune function. Deller noted that reactive astrocytes rapidly secrete extracellular matrix molecules into the denervated outer molecular layer of the fascia dentata after an entorhinal cortex lesion. These molecules form a boundary that could prevent the ingrowth of fibers from adjacent areas into the deafferented zone. Thus, extracellular matrix molecules could define growth boundaries for sprouting axons and could contribute to the layer-specific sprouting of surviving afferents in this lesion paradigm. Michael Frotscher discussed the more general question of why entorhinal fibers are restricted to terminating on the distal dendrites of hippocampal cells during development. He showed that the signals guiding this layered development are preserved in cell culture preparations, and involve a sequence of pathfinder cells that mostly die after laminar development is complete.

Fred Gage considered the general issue of neurogenesis, and the possibility of increasing it as a function of appropriate experience. Stem cells, harvested from a variety of sources, seek out target zones, and form appropriate synaptic contacts. The target area can dictate the fate of these new cells, whose functionality, however, remains to be determined. Environmental enrichment increased the survival of new cells, but did not increase neurogenesis per se. On the other hand, activity (running in a wheel) increased neurogenesis without affecting survival rate. Subsequent behavioral tests suggested that the increased neurogenesis had functional consequences. These results, in conjunction with the recent report of neurogenesis in neocortical circuits, indicate a great deal more plasticity in the central nervous system than would have been thought a decade or two ago.

Finally, a group of presenters considered the functions of various structures within the parahippocampal region, based on recording studies in rats, neuroimaging in humans, and lesion studies in rats and monkeys. One general question that could be raised about the various parts of the parahippocampal and hippocampal regions is whether they subserve essentially the same function, as some have supposed, or have rather different functions, as others have suggested. The overwhelming impression conveyed by these speakers is that the different components of these systems play rather different roles. Howard Eichenbaum, for example, showed that single neurons recorded from the perirhinal and entorhinal cortex had rather different characteristics than neurons recorded from the hippocampus proper. In lesion work, he showed that while fornix lesions did not induce a delay-dependent deficit in an odor-based recognition task, lesions in the parahippocampal region did. Betsy Murray reported on lesion studies with monkeys, using visual recognition and associative learning tasks. Rhinal cortex (entorhinal plus perirhinal) lesions had the most severe effect, followed by parahippocampal cortex lesions. Ibotenate lesions of the amygdala and hippocampus did not impair recognition memory at all. In the associative task, aspiration lesions of the hippocampus or amygdala alone had no effect, whereas lesions of the rhinal cortex caused a significant impairment. She concluded that the rhinal cortex in monkeys is involved in the equivalent of “semantic memory” in humans, and hence is important for stimulus identification, stimulus recognition, and stimulus-stimulus association.

Wendy Suzuki reported on single-neuron recording studies in monkeys while performing a recognition task. Neurons throughout the entorhinal and perirhinal cortices responded to all aspects of the task, including the match condition, the nonmatch condition, and various aspects of the delay interval. Comparing her work with related studies in humans, Suzuki concluded that the hippocampus also makes a contribution to recognition memory, but only under some conditions. One possibility that was discussed by a number of participants was that the hippocampus encodes the context within which the recognition task unfolds.

John Gabrieli reviewed a series of functional MRI studies during which subjects either encoded or retrieved scene information. Activation was observed in the posterior parahippocampal cortex during encoding of novel scenes, but no anterior activations were seen (perhaps in the subiculum) during successful retrieval. In another task, employing an event-related fMRI protocol, subjects were shown novel slides, and asked to indicate whether they were indoor or outdoor scenes. A subsequent unexpected memory test allowed Gabrieli to ask which brain areas had been activated for items that were successfully retrieved. Among the areas whose activity predicted retrieval were the parahippocampal and prefrontal cortices. Finally, in a stem completion task, correlations were seen between activation in the entorhinal cortex and successful recall, but in a way that suggested that this activity reflected a kind of “state modulation” that had prepared the subject to learn.

This notion converged rather nicely with the presentation by Michael Hasselmo, who focused on cholinergic modulatory effects in the entorhinal cortex. He speculated that varied levels of ACh could reflect different functional states of the entorhinal region. In a computational model, shifts from low to high ACh allowed spiking in entorhinal “units” that mirrored the kind of activity seen in Eichenbaum’s studies. Further, high levels of ACh could reflect a process of reactivation-induced consolidation, by influencing the extent to which information can flow from hippocampus to cortex, or vice versa.

Overall, the meeting conveyed the sense of an area bursting with exciting results, still lacking a conclusive conceptual framework, but well worth the new attention it is receiving. That the parahippocampal region is critically involved in learning and memory seems beyond doubt. That this region is centrally implicated in many neuropathological conditions is also clear. How to tie all these exciting developments together is a task for the future. This meeting brought that future a little closer.