

The anatomy, physiology and functions of the perirhinal cortex

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The perirhinal cortex is a polymodal association area that contributes importantly to normal recognition memory. A convergence of recent findings from lesion and electrophysiological studies has provided new evidence that this area participates in an even broader range of memory functions than previously thought, including associative memory and emotional memory, as well as consolidation functions. These results are consistent with neuroanatomical research showing that this area has strong and reciprocal connections with widespread cortical sensory areas and with other memory-related structures, including the hippocampal formation and amygdala.

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Abbreviations

DMS delayed matching to sample task
DNMS delayed non-matching to sample task

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Introduction

The ability to store new memories for facts and events is referred to as declarative memory and is a form of memory known to be critically dependent on the integrity of the medial temporal lobe (i.e. the hippocampus and surrounding cortical structures) [1,2*]. Systematic lesion studies carried out in monkeys and rats over the past 15 years have sought to identify the specific medial temporal lobe structures underlying declarative memory function. Whereas early studies focused on the role of the hippocampus, recent findings indicate that the surrounding cortical regions, including the entorhinal, perirhinal, and parahippocampal cortices, contribute as much as, or perhaps even more than, the hippocampus to certain forms of declarative memory. Of these surrounding cortical areas, the greatest attention has been focused on the mnemonic functions of the perirhinal cortex. A convergence of studies from the domains of neuroanatomy, neurophysiology and neuropsychology have made substantial progress in delineating the contributions of the perirhinal cortex to memory as well as to sensory functions.

The following review focuses on current advances in our understanding of the neuroanatomy, physiology and functions of the perirhinal cortex, resulting primarily from experimental studies in monkeys and rats. I will first

discuss findings from neuroanatomical studies examining the boundaries and connectivity of the perirhinal cortex. I will then consider evidence from behavioral and electrophysiological studies examining the contribution of this area to a variety of different functions, including sensory/perceptual functions, recognition memory, associative memory, emotional memory and consolidation.

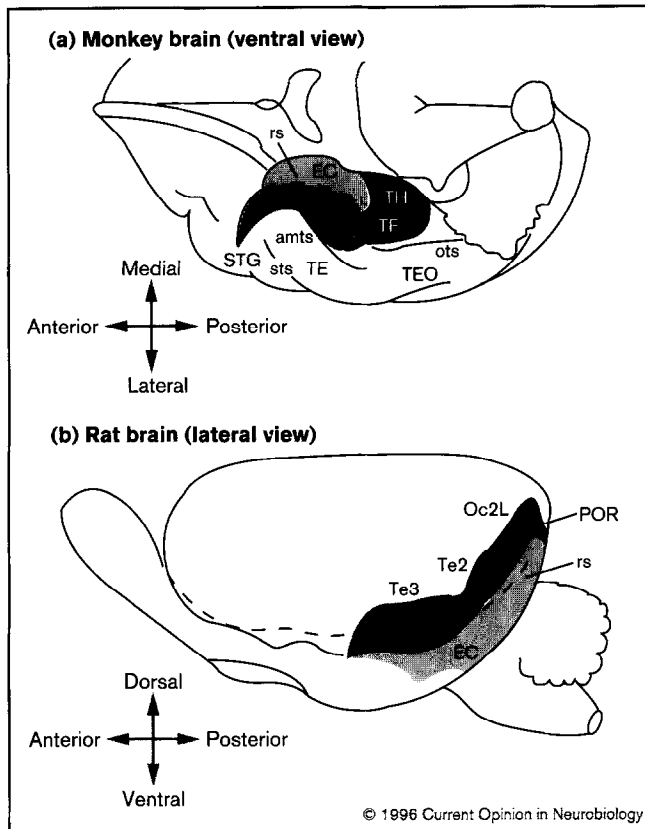
Neuroanatomy of the perirhinal cortex

Recent neuroanatomical studies in the macaque monkey have revealed that the perirhinal cortex is characterized by strong interconnections with diverse unimodal and polymodal cortical association areas, as well as with the hippocampal formation and the amygdala [3,4**,5**]. Less information is available concerning the neuroanatomical organization of the rat perirhinal cortex, but a recent review of the literature by Burwell *et al.* [6**] suggests that the same general patterns of connectivity apply. Whereas early studies relied exclusively on cytoarchitectonic criteria to define the boundaries of the perirhinal cortex [7,8], the advent of modern neuroanatomical tracing techniques have provided more objective connectional criteria for delineating this area.

The perirhinal cortex in both monkeys and rats is composed of two cytoarchitectonically distinct areas (areas 35 and 36) originally described by Brodmann [7]. In monkeys, perirhinal areas 35 and 36 form a band of cortex situated lateral to the full extent of the rhinal sulcus (Figure 1a) [5**]. On the ventral surface of the brain, the perirhinal cortex includes much of the inferotemporal gyrus (i.e. the band of cortex situated between the anterior middle temporal sulcus and the rhinal sulcus). The perirhinal cortex also extends anteriorly to include the medial portion of the temporal pole. The boundaries of the perirhinal cortex in rats have varied substantially in the literature. Burwell *et al.* [6**] have proposed that the rat perirhinal cortex surrounds the posterior portion of the rhinal sulcus (Figure 1b). As in monkeys, it is bounded medially by the entorhinal cortex and laterally by temporal association areas. The posterior boundary of the rat perirhinal cortex is formed by a region these authors have termed the postrhinal cortex, which has connectional similarities with the parahippocampal cortex (areas TH and TF) in monkeys [6**].

The perirhinal cortex in both monkeys and rats is defined by three major connectional features. The first is its robust interconnections with the hippocampal formation via the entorhinal cortex [4**,6**,9,10,11*]. Approximately 40% of the direct input to the entorhinal cortex arises from the adjacent perirhinal cortex and terminates primarily in its anterior and lateral regions in monkeys [4**,10,11*]. The perirhinal cortex also receives robust return projections

Figure 1



Perirhinal cortex of monkey and rat. **(a)** Ventral surface view of the monkey brain and **(b)** lateral surface view of the rat brain showing the boundaries of the perirhinal (areas 35 and 36), entorhinal (EC), and parahippocampal (areas TH and TF) or postrhinal (POR) cortices (adapted from Burwell *et al.* [6**]). Note that area 35 in monkeys is buried within the rhinal sulcus (rs) and is not visible from a surface view. amts, anterior middle temporal sulcus; Oc2L, secondary visual cortex; ots, occipitotemporal sulcus; STG, superior temporal gyrus; sts, superior temporal sulcus; Te2 and Te3, temporal cortex. (Areas TH, TF and TE of von Bonin and Bailey [60].)

from the entorhinal cortex that originate in the same region to which the perirhinal cortex projects [4**]. A similar pattern of connectivity has been described in rats [6**]. All levels of the rat perirhinal cortex project to the entorhinal cortex and terminate most strongly in its lateral regions.

The second defining feature of the perirhinal cortex is its prominent inputs from diverse unimodal and polymodal association cortices [5**,9,11*,12,13]. Recent quantitative neuroanatomical studies in monkeys have provided new details concerning the organization and topography of the cortical inputs to this area [5**,11*]. The most prominent inputs to the monkey perirhinal cortex arise in the laterally adjacent unimodal visual areas TE and TEO. The second strongest input originates in the parahippocampal cortex (areas TH and TF). More modest inputs originate in somatosensory association areas of the insular cortex, putative auditory association areas in the anterior superior temporal gyrus and polymodal cortical areas, including the

orbitofrontal cortex and the dorsal bank of the superior temporal sulcus.

Even though comparable tract-tracing studies focused on the rat perirhinal cortex have yet to be carried out, the available information suggests that this region receives a similar convergence of multimodal sensory information [6**]. Compared to the monkey perirhinal cortex, which receives particularly prominent projections from visual areas, the rat perirhinal cortex appears to receive more evenly distributed projections from somatosensory, auditory and olfactory association areas, with weak inputs from visual areas [6**]. Polymodal areas projecting to the rat perirhinal cortex include the medial and ventrolateral prefrontal cortex, as well as the anterior cingulate, retrosplenial and postrhinal cortices. Even though currently available information suggests that the cortical efferents of the perirhinal cortex in rats and monkeys generally reciprocate their cortical afferents, the relative strength or precise topography of these projections has not been extensively examined in either species.

The third defining feature of the perirhinal cortex is its prominent interconnections with the amygdaloid complex. In monkeys, the polar portion of the perirhinal cortex has powerful and reciprocal connections with a number of amygdaloid nuclei, including the lateral, basal and accessory basal nuclei (L Stefanacci *et al.*, *Soc Neurosci Abstr* 1994, 20:34; [3,11*]). Weaker projections originate in the medial nucleus and periamygdaloid cortex. The more ventrocaudally situated regions of the perirhinal cortex tend to have weaker interconnections directed primarily to the lateral and basal nuclei, and receive weak to moderate projections from the accessory basal nucleus. In rats, the perirhinal cortex has its strongest interconnections with the lateral nucleus, although minor reciprocal connections with the accessory basal nucleus have also been described [6**].

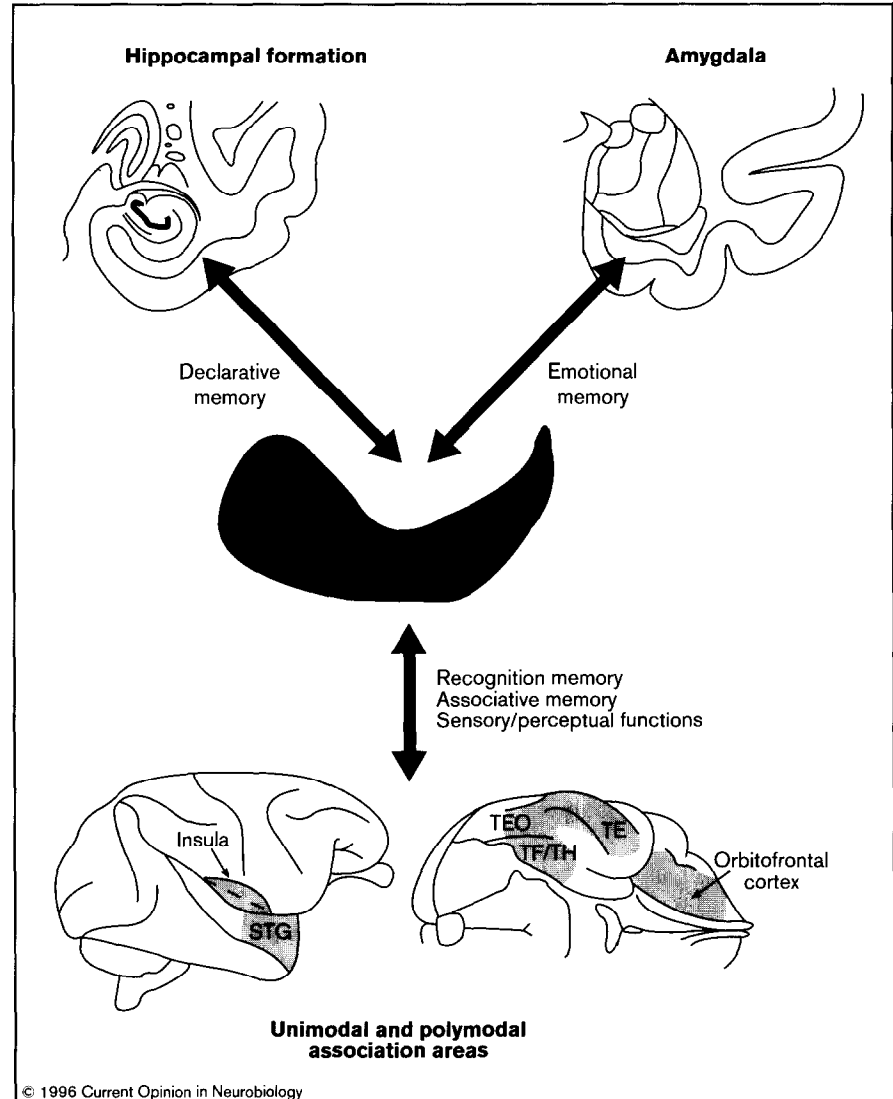
Taken together, these neuroanatomical data suggest that the perirhinal cortex in both monkeys and rats is a zone of convergence from both higher order sensory association areas as well as a number of different subcortical structures (Figure 2). From a functional perspective, this pattern of connectivity suggests that the perirhinal cortex is in a unique position to synthesize diverse sensory information as well as to interact with other memory-related structures, including the hippocampus and the amygdala.

Sensory properties of perirhinal neurons

Consistent with neuroanatomical reports, early physiological studies in the anesthetized monkey showed that neurons in the perirhinal cortex responded to visual, somatosensory, auditory or a combination of sensory stimuli [14]. Physiological studies in the rat perirhinal cortex have identified both odor-responsive (BJ Young *et al.*, *Soc Neurosci Abstr* 1995, 21:375) and visually responsive [15*] neurons.

Figure 2

Schematic diagram of the connections and functions of the perirhinal cortex. The perirhinal cortex is shown as an unfolded, two-dimensional representation of the cortical surface area in the monkey brain. Shaded areas on the lateral and ventral views of the cortex indicate some of the strongest cortical inputs to the monkey perirhinal cortex. The lateral sulcus has been 'opened up' to reveal the insular cortex on the lateral surface view of the brain. The cortex of the dorsal bank of the superior temporal sulcus and the cingulate cortex, both of which project to the perirhinal cortex, cannot be seen on these surface views.



Recent studies carried out in the behaving monkey have described some of the visual response properties of perirhinal neurons in more detail [16,17,18*]. These studies showed that perirhinal neurons, like neurons in the adjacent unimodal visual area TE [19**], responded in a highly selective way to certain classes of visual stimuli (i.e. they were stimulus selective) [16,17,18*]. Typically, perirhinal neurons responded best to highly complex colored stimuli; however, no attempt has been made to rigorously characterize the optimal stimulus for these neurons (but see [18*]). Like responses of neurons in area TE [19**], the visual responses of perirhinal neurons were invariant for changes in size or location [17].

Recently, Gaffan and colleagues [20**,21**] provided evidence that lesions including the perirhinal cortex produce a mild impairment in monkeys' ability to discriminate among large numbers, but not small numbers of complex visual stimuli. On the basis of these findings,

the authors argued that the perirhinal cortex participates in certain sensory/perceptual functions, including object identification. This interpretation, however, should be considered tentative because of the mild nature of the observed deficit (1–11% differences in scores of normals versus lesioned animals on tasks A, A1 and D of [20**]). The relationship between the sensory properties of perirhinal neurons described above and the mild discrimination deficit resulting from lesions including the perirhinal cortex [20**,21**] remains to be explored.

The role of the perirhinal cortex in recognition memory

Recognition memory is defined as the successful identification of a stimulus that has been presented previously. In the animal literature, this form of memory has often been assessed using a 'trial unique' version of the delayed matching or non-matching to sample task (abbreviated DMS or DNMS, respectively). In this task, animals are

given the choice between a novel stimulus and a sample stimulus that had been presented earlier. Novel or 'trial unique' stimuli are used on each trial. Depending on which version of the task is used, the experimental animal chooses either the 'matching' stimulus or the novel 'non-matching' stimulus to receive a food reward. Memory is assessed by increasing the delay interval between the sample and the choice presentations.

A consistent finding from the monkey and rat literature has been that relative to control animals, animals with lesions including the perirhinal cortex perform more poorly on the DNMS task, and often forget rapidly the sample stimulus [20••,21••,22–26,27•]. Although these lesions have typically included damage to the perirhinal cortex along with adjacent structures (i.e. hippocampal, entorhinal or parahippocampal cortices), recent studies suggest that the perirhinal damage may be responsible for a substantial portion of the observed recognition memory impairment.

Gaffan [21••] and Meunier *et al.* [24] have found that selective lesions of the perirhinal cortex in monkeys produce significant memory impairment on either a DMS or DNMS task. In contrast, lesions limited to the entorhinal [28••] or parahippocampal cortex (S) Ramus *et al.*, *Soc Neurosci Abstr* 1994, 20:444) produce either a transient impairment or no impairment, respectively.

Alvarez *et al.* [29•] have shown that lesions of the hippocampal region (i.e. dentate gyrus, hippocampus proper and subicular complex) produce a mild and enduring memory impairment on the DNMS task, although this impairment appears to be less severe than that following perirhinal lesions [24]. Thus, compared to other more restricted lesions of medial temporal lobe structures, damage limited to the perirhinal cortex appears to have the most devastating effect on visual recognition memory.

Although the majority of studies have examined the effect of perirhinal lesions on recognition memory for visual stimuli, the memory impairment is not limited to the visual modality. For example, lesions including the perirhinal cortex impair memory for tactual information in monkeys [25] and for olfactory information in rats [30]. Recent studies have shown that recognition memory for spatial locations is also affected by damage to the perirhinal cortex [31•,32,33••]. Selective lesions of the perirhinal cortex or combined perirhinal–entorhinal lesions in rats produced impairments on the performance of a number of different place navigation tasks. In cases in which the performance was assessed over a range of delay intervals, rats with perirhinal lesions exhibited rapid forgetting of spatial information relative to control animals [31•,33••].

Not all forms of spatial memory, however, are impaired by perirhinal damage. Gaffan [21••] showed that monkeys

with selective perirhinal lesions were unimpaired on a simple spatial discrimination task. Taken together, these findings are consistent with the known connectivity of the perirhinal cortex and support the idea that this region contributes importantly to recognition memory in all modalities thus far tested, as well as certain forms of spatial memory.

The neural correlates of recognition memory

Examination of the response properties of neurons in the perirhinal cortex and surrounding cortical areas in the behaving monkey have revealed a variety of neural mechanisms that may play a role in recognition memory. In addition to the sensory-related perirhinal neurons described above, the responses of another subpopulation of memory-related perirhinal neurons were modulated by information held in memory. Typically, these neurons responded better to some novel stimuli than to others (i.e. they were stimulus selective). These selective responses steadily declined as the stimulus gradually became more familiar [34–36]. This response decrement with stimulus repetition, referred to as the 'familiarity effect', has been observed with delays of up to 24 hours between consecutive stimulus presentations [34].

Recently, similar familiarity effects have been reported in both anesthetized and awake rats [15•,37]. Indeed, such information could serve as a cue to solve a commonly used version of the DNMS task in which the animals are asked to differentiate between a novel stimulus and a stimulus that has been seen only once before (i.e. 'trial unique' DNMS). The duration of the neuronal familiarity signal (i.e. observed following delays of up to 24 hours [34]) is consistent with the delay intervals at which animals with perirhinal lesions are typically impaired [24]. The characteristics of this familiarity signal also allow for the possibility that it may be contributing to other forms of memory, including repetition priming [38].

In a working memory version of the DMS task in which stimulus familiarity could not be used as a cue to solve the task, a different neural mechanism was described that may also participate in working and/or recognition memory [39]. In this task, the monkey was required to keep the first 'sample' stimulus in mind and respond only to the repetition of that stimulus, but not to repetitions of other intervening stimuli. During the performance of this task, a subpopulation of perirhinal neurons (35% of the neurons showing memory effects) signaled the occurrence of the matching stimulus with an enhanced response. This response enhancement was observed only for the to-be-remembered stimulus. Moreover, an examination of the time course of the match-enhancement signal showed that it occurred well before the behavioral response of the animal, suggesting that this matching signal could be used by the animal to perform the task.

Another neural mechanism that may participate in working or recognition memory involves sustained stimulus-selective neuronal activity during the delay period of the DMS task [40,41]. Such delay activity has recently been observed in the rat perirhinal cortex during the performance of a continuous delayed match to odor task (BJ Young *et al.*, *Soc Neurosci Abstr* 1995, 21:375).

While delay activity may participate in encoding of the to-be-remembered stimulus in tasks with no intervening stimuli, the presentation of even one intervening stimulus between the sample and the match disrupts this sample-selective delay activity in the monkey perirhinal cortex [16]. It remains to be determined whether this mnemonic signal carried by delay activity is specific to situations with no intervening stimuli or is an example of a broader category of memory-related responses of perirhinal neurons.

The role of the perirhinal cortex in associative memory and consolidation

Associative memory has been examined in animals by teaching them to associate randomly chosen pairs of stimuli with each other. In some studies, animals are presented with one element of the pair and are asked to choose the correct paired associate. Combined lesions of the perirhinal and entorhinal cortices in either monkeys [42] or rats [43] produced severe impairments in the retention of previously learned paired associates, as well as in the learning of new paired associates. In physiological studies in which the recording sites included both the lateral portion of the perirhinal cortex as well as medial portions of area TE, Sakai and Miyashita [44] described 'pair-coding' neurons that responded maximally to both members of particular paired stimuli. This population of pair-coding neurons in the perirhinal cortex and area TE appear to participate in the long-term representation of visual paired associates.

Recently, Higushi and Miyashita [45••] provided evidence that back-projections from the perirhinal and/or entorhinal cortices are critical for the maintenance or consolidation of pair-coding information in area TE. A commonly held view is that the structures of the medial temporal lobe are involved in consolidation of information via prominent back-projections to the cortical sensory areas that originally processed the information. These sensory areas are thought to act as final repositories for long-term memories [1,46,47,48••].

Consistent with this hypothesis, monkeys with unilateral lesions of the entorhinal and perirhinal cortices no longer exhibited significant pair-coding activity in the ipsilateral area TE [45••]. While other studies have shown that the hippocampus and entorhinal cortex are important for the consolidation of a variety of different kinds of information, including emotional information [49], spatial information [50] and conditioned eye-blink information

[51•], the study by Higushi and Miyashita [45••] suggests that the perirhinal cortex should be included in the subset of medial temporal lobe structures participating in consolidation of visual paired associate information.

The perirhinal cortex and fear conditioning

Fear conditioning is a paradigm in which a neutral stimulus acquires the ability to evoke strong emotional responses following temporal pairing with an aversive stimulus. This form of memory, extensively examined in rats, is known to be critically dependent on the integrity of the amygdaloid complex [52••]. Although little information is available concerning the neural substrates of fear conditioning in monkeys, recent studies in rats suggest that the perirhinal cortex may participate. In contrast to lesions of the amygdala, which disrupt fear conditioning following either pre- or post-operative training procedures [53•], the effects of perirhinal damage on fear conditioning are strongly dependent on whether the lesion is made before or after training. Pre-training lesions of the perirhinal cortex that also included either adjacent temporal cortex [54,55] or the entorhinal cortex [56] do not interfere with conditioning to auditory or contextual cues. In contrast, post-training perirhinal lesions significantly disrupt conditioning to visual [57,58••], auditory [58••], as well as contextual [59••] cues.

These findings make several important points. First, since pre-training lesions of the perirhinal cortex did not affect fear conditioning, this suggests that normal acquisition and expression of conditioned fear can be carried out through other neural pathways. Second, the attenuation of fear conditioning following post-training perirhinal lesions suggests that in the intact brain, this area is involved in the storage, consolidation or retrieval of emotional memories. Further studies will be needed to differentiate between these possibilities. Third, the finding that perirhinal lesions can effect conditioning to visual, auditory or contextual cues is consistent with neuroanatomical data showing this area is a zone of convergence for both unimodal and complex polymodal information [6••]. Finally, while the perirhinal cortex has typically been associated with the declarative or explicit memory system (including the hippocampal formation), these data suggest that this area may also participate in the emotional memory system along with the amygdala. Indeed, the perirhinal cortex may be an important interface of interaction for both the declarative and emotional memory systems (Figure 2).

Conclusions

Findings from multidisciplinary studies in monkeys and rats have shown that the perirhinal cortex participates in a wide range of memory functions, including recognition memory, associative memory, and emotional memory, as well as consolidation functions. Importantly, neuro-anatomical, physiological and lesion studies focused on the perirhinal cortex in both monkeys and rats have revealed

consistent and parallel findings, suggesting that this area contributes to similar functions in both species.

While these studies have provided important clues to understanding the functional organization of the perirhinal cortex, they also serve to highlight some of the fundamental questions that remain. For example, whereas some studies have demonstrated memory impairment following lesions limited to the perirhinal cortex [21••,24,31•,59••], the most profound memory deficits have often been observed following combined lesions of the perirhinal and entorhinal cortices [20••,24,27•] or perirhinal and parahippocampal cortices [23,25]. What is the relative contribution of these anatomically distinct [11•] cortical areas to memory?

There have also been exciting advances in our understanding of the neural correlates of memory in the perirhinal cortex. A causal relationship between a particular neural mechanism and memory performance, however, has yet to be established. The findings of Higushi and Miyashita [45••] suggest that back-projections from the perirhinal cortex to area TE participate in the consolidation of visual associative memories. These findings raise further questions concerning the nature and time course of the feedback signals from perirhinal cortex to area TE that serve to establish these long-term associative memories. Further multidisciplinary studies in monkeys and rats combined with computational approaches will be important in addressing these many outstanding questions.

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