The Perirhinal Cortex

Wendy A. Suzuki[1] and Yuji Naya[2]

[1]Center for Neural Science, New York University, New York, NY 10003;
email: wendy@cns.nyu.edu

[2]Department of Psychology, Peking-Tsinghua Center for Life Sciences and
PKU-IDG/McGovern Institute for Brain Research, Peking University, Beijing 100871,
China; email: yujin@pku.edu.cn

Keywords

association memory, declarative memory, medial temporal lobe

Abstract

Anatomically, the perirhinal cortex sits at the boundary between the medial
temporal lobe and the ventral visual pathway. It has prominent interconnec-
tions not only with both these systems, but also with a wide range of unimodal
and polymodal association areas. Consistent with these diverse projections,
neurophysiological studies reveal a multidimensional set of mnemonic sig-
nals that include stimulus familiarity, within- and between-domain associ-
ations, associative recall, and delay-based persistence. This wide range of
perirhinal memory signals not only includes signals that are largely unique
to the perirhinal cortex (i.e., object familiarity), consistent with dual-process
theories, but also includes a range of signals (i.e., associative flexibility and
recall) that are strongly associated with the hippocampus, consistent with
single-process theories. These neurophysiological findings have important
implications for bridging the gap between single-process and dual-process
models of medial temporal lobe function.

Contents

INTRODUCTION

In primates, the perirhinal cortex lies on the ventral-medial surface of the temporal lobe surrounding the amygdala and anterior hippocampus (**Figure 1**). Brodmann was one of the first to describe the unique cytoarchitectonic features of the perirhinal cortex more than 100 years ago (Brodmann 1909). However, only relatively recently have we started to appreciate the full extent of the contributions of the perirhinal cortex to a range of higher cognitive functions. Findings from a combination of behavioral lesion studies (Murray et al. 1989, Zola-Morgan et al. 1989, Suzuki et al. 1993) and tract-tracing studies (Suzuki & Amaral 1994a,b; Suzuki & Amaral 2003) in nonhuman primates first identified the perirhinal cortex as contributing importantly to visual recognition memory. Since then, extensive work in both humans (Ranganath & Ritchey 2012) and animal model systems (Brown et al. 2010) has focused on specifying the mnemonic functions of the perirhinal cortex with a major emphasis on its contributions to recognition memory.

Recognition memory is thought to comprise two major components: recollection and familiarity. Recollection is defined as memory of the specific contextual details of a particular event or episode, whereas familiarity is defined as awareness of an item having been presented previously without access to additional contextual information about the event. Early physiology studies in monkeys showed that perirhinal cells respond selectively to particular visual stimuli and signal the prior occurrence of that preferred visual stimulus with a decreased response upon stimulus repetition (Brown & Aggleton 2001, Brown et al. 2010, Aggleton et al. 2012). This prominent so-called familiarity signal indicates that the perirhinal cortex is likely involved in a familiarity process as suggested by dual-process models of medial temporal lobe (MTL) function (Davachi 2006, Diana et al. 2007, Eichenbaum et al. 2007, Mayes et al. 2007). These models suggest that familiarity and recollection are distinct forms of memory that are supported by different brain areas; the perirhinal cortex is essential for object familiarity, and the hippocampus is important for recollection that includes contextual and spatial associative memories. Perirhinal-based memories are often conceptualized as important for encoding individual items or objects in memory, whereas the hippocampus is important for associating those items in memory (Murray & Richmond 2001, Davachi 2006, Staresina & Davachi 2008).

Another influential view suggests that the perirhinal cortex contributes to a wide range of functions, including both familiarity and recollection (Squire et al. 2007). This view argues for considerable cooperation between the different MTL structures for both recollection and familiarity (Squire et al. 2007), although the extent to which each area specifically contributes may differ. Moreover, these authors suggest that rather than trying to understand the MTL through the relatively narrow lens of recognition memory, a more fruitful strategy is to focus on specific
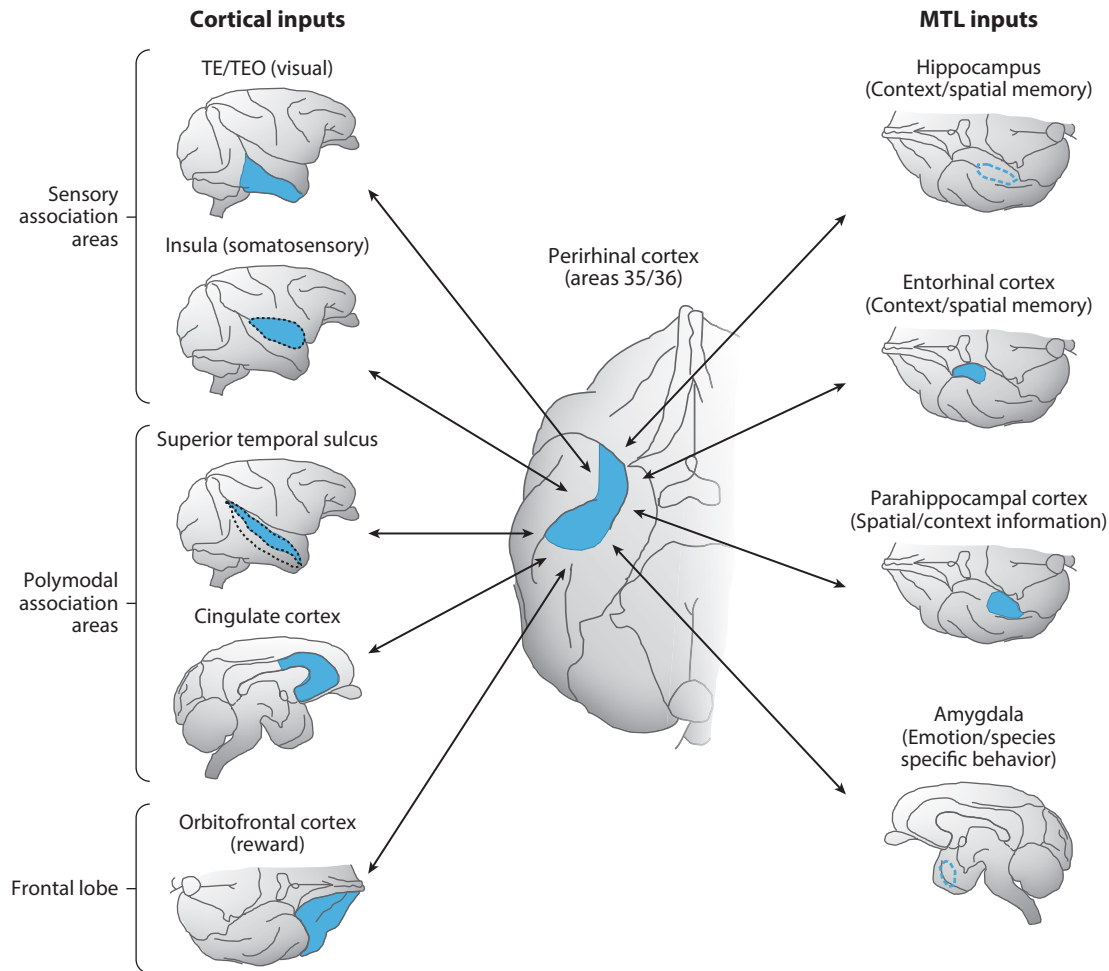
Figure 1

Schematic illustration of the cortical and medial temporal lobe (MTL) connections of the monkey perirhinal cortex (areas 35 and 36).

stimulus attributes of memory and how they are represented in particular MTL areas. We follow this latter approach in our current analysis of the functions of the perirhinal cortex.

In this article, we offer a new view of perirhinal function consistent with its full complement of anatomical projections and neurophysiological response properties. We argue that its prominent and convergent projections from sensory, polymodal, and reward-related cortical areas together with its prominent interconnections with other MTL structures suggest that the perirhinal cortex is designed to associate information in memory across multiple domains and modalities. Consistent with this region's anatomical connections, neurophysiological studies have described not only its prominent visual familiarity responses, but also various associative learning, memory, and recall signals as well as demonstrating striking persistent delay activity across a range of different domains (**Table 1**). We discuss this new view of perirhinal functions in the context of dual-process and single-process models of MTL function. We also address the evidence supporting the role of the perirhinal cortex in visual perception.

Table 1 The memory functions of the perirhinal cortex

Mnemonic category	Neural signal	Behavioral role
Familiarity	Repetitive suppression	Recognition memory[a]
Association		
Within domain (item and item)		
Coding	Un-unitized pair-coding cells (area 36), unitized pair-coding cells (area 35)	Semantic linkage, concepts, higher-order perception[b]
Recall	Pair-recall cells	Flexible associative recall[c]
Between domains		
Item and place, time, or context	Changing cells, object-time cells, object-context signals	Relational memory[d]
Item, configuration, and reward	Object-reward cells, reward condition cells	Expectation of reward[e]
Maintenance over trace interval	Persistent activity for single or multiple items	Conditioning memory, higher-order perception[f]
Information gating	Selective facilitation of signal transfer	Emotional enhancement of memory[g]

[a]Xiang & Brown 1998, Diana et al. 2007, Eichenbaum et al. 2007.
[b]Fujimichi et al. 2010, Bussey & Saksida 2007, Naya et al. 2003a.
[c]Sakai & Miyashita 1991, Naya et al. 2001, Hirabayashi et al. 2013a.
[d]Yanike et al. 2009, Naya & Suzuki 2011, Watson et al. 2012.
[e]Liu & Richmond 2000, Mogami & Tanaka 2006, Ohyama et al. 2012.
[f]Kent & Brown 2012, Naya et al. 2003b, Bussey & Saksida 2007.
[g]Paz et al. 2006, Fernandez & Tendolkar 2006.

THE ANATOMY OF THE PERIRHINAL CORTEX

The perirhinal cortex is composed of two major subdivisions, a smaller and medially situated area 35 and a much larger, laterally situated area 36. Early anatomical studies from the 1970s first identified the perirhinal cortex in monkeys as an area that received inputs from multiple sensory modalities, although the full extent of its connections was not known (Jones & Powell 1970, Van Hoesen & Pandya 1975). Since those early reports, substantial progress has been made in understanding the major cortical and subcortical projections of the perirhinal cortex in monkeys (Suzuki & Amaral 1994a, Lavenex et al. 2004). This region is defined by two major categories of inputs. First, it has major connections with other adjacent regions of the MTL, including, in order of descending strength, the entorhinal cortex, the parahippocampal cortex, the amygdala, and the hippocampus. Second, the perirhinal cortex is defined by its prominent interconnections with a wide range of unimodal and polymodal cortical association areas. The anatomical connections of the perirhinal cortex in rodents are similar though not identical and are not discussed in detail here (Burwell & Amaral 1998, Suzuki 2009a).

Medial Temporal Lobe Connections

One of the strongest MTL connections of the monkey perirhinal cortex is with the entorhinal cortex. The perirhinal projections terminate in a large extent of the entorhinal cortex that includes a wide medial-lateral portion of the anterior entorhinal cortex and more restricted projections to the lateral portions of mid and caudal levels of the entorhinal cortex (Insausti et al. 1987, Suzuki & Amaral 1994b, Mohedano-Moriano et al. 2008). These inputs follow a feedforward projection pattern terminating mainly in superficial layers I–III as well as in layer V (Suzuki &

Amaral 1994b, Mohedano-Moriano et al. 2008). Projections from the entorhinal cortex back to the perirhinal cortex are also prominent and exhibit a medial-lateral topography such that the most lateral portions of the anterior entorhinal cortex project to the most medial portions of the perirhinal cortex (i.e., area 35 and medial portions of area 36), whereas the medial portions of the anterior entorhinal cortex project to the lateral perirhinal cortex (Suzuki & Amaral 1994b, Muñoz & Insausti 2005). These projections follow a classic feedback projection pattern originating mainly from layer V, with weaker involvement of layers VI and III, and terminating in and around perirhinal layer II as well as in layers V and VI (Suzuki & Amaral 1994b, Muñoz & Insausti 2005).

A second major MTL input to the perirhinal cortex comes from the posteriorly adjacent parahippocampal cortex (areas TH and TF). The parahippocampal cortex is an area of polymodal convergence receiving input from ventral stream visual areas TEO and TE and visuospatial input from retrosplenial cortex and posterior parietal cortex, as well as input from auditory association areas (Suzuki & Amaral 1994a). Unlike the rest of the MTL projections to the perirhinal cortex, the projections from the parahippocampal cortex are not strongly reciprocal; the perirhinal cortex receives more prominent projections from the parahippocampal cortex than it sends back (Suzuki & Amaral 1994a, Lavenex et al. 2004).

One major set of MTL projections to the perirhinal cortex that tends to be overlooked in considering the functions of the perirhinal cortex is its prominent interconnections with the amygdala (Stefanacci et al. 1996). These projections exhibit a rostrocaudal gradient whereby the most anterior and ventral regions of the perirhinal cortex receive the strongest amygdala projections and the caudal perirhinal cortex has only weak interconnections with the amygdala. These projections are largely reciprocal and are directed primarily to the lateral and basal nuclei of the amygdala.

The perirhinal cortex also has direct interconnections with the hippocampus and subicular complex. However, the absolute strength of these latter interconnections (estimated using number of labeled cells from retrograde tracer studies) is substantially weaker than its connections with the entorhinal cortex, the parahippocampal cortex, or the amygdala. For nearly its entire rostrocaudal extent, cells in the most distal portions of area CA1 and the most proximal portions of the subiculum project to the perirhinal cortex (Yukie 2000, Insausti & Muñoz 2001). Insausti & Muñoz (2001) have described a weak projection from the presubiculum to the perirhinal cortex. Both these projections are reciprocal (Suzuki & Amaral 1990, Yukie 2000); they provide a direct route by which the perirhinal cortex can influence and be influenced by hippocampal/subicular activity in addition to the prominent indirect connections with these regions provided by the entorhinal cortex.

Cortical Connections

In addition to its major connections with structures within the MTL, the perirhinal cortex is also characterized by its prominent interconnections with a range of both unimodal and polymodal association areas (Suzuki & Amaral 1994a, Lavenex et al. 2002). The strongest cortical input to the perirhinal cortex in monkeys comes from the adjacent unimodal visual areas TE and TEO. Other projections to the perirhinal cortex include input from polymodal regions on the dorsal bank of the superior temporal sulcus, somatosensory input from the insular cortex, and frontal lobe inputs originating from lateral and orbital areas 11, 12, and 13. These orbitofrontal areas have been implicated in reward-related processing (de Araujo et al. 2003, Padoa-Schioppa & Assad 2006, Chaudhry et al. 2009). The perirhinal cortex tends to project back to a much wider extent of the cortex than it receives input from, including some areas that do not project to it at all (Lavenex et al. 2002). This striking asymmetric reciprocity may be related to its prominent role in associative memory recall (see Within-Domain Associations, below).

THE FUNCTIONAL ORGANIZATION OF THE PERIRHINAL CORTEX

Memory

Many previous physiology studies in both monkeys and rodents show that neurons in the perirhinal cortex respond selectively to particular visual objects and demonstrate that this stimulus-selective response is suppressed with repetition (Xiang & Brown 1998, Aggleton et al. 2012) (**Table 1**). This familiarity signal has been described in rodents, monkeys, and humans and reviewed extensively in the literature (Brown et al. 2010, Aggleton et al. 2012). We do not expand on these well-described familiarity signals. Instead, we highlight perirhinal mnemonic signals beyond simple visual object familiarity. In particular, we focus on its role in within-domain (i.e., item-item) and between-domain associations as well as on the growing evidence for its contribution to aspects of conditioning via its interconnections with the amygdala (**Table 1**).

Within-domain associations. A major tenet of dual-process theories is the idea that a unique function of the hippocampus is its ability to encode the relationship between items and events that occur together through flexibly accessible associative links (Eichenbaum & Cohen 2001, Staresina & Davachi 2009). In particular, the hippocampus has the ability to recall the associative link when presented with one item of a learned pair (Polyn et al. 2005, Foster & Wilson 2006, Kuhl et al. 2011). Although extensive evidence supports the important contributions of the hippocampus to associative, relational, and recall functions (Davachi 2006, Eichenbaum et al. 2007), strong neurophysiological evidence also indicates that perirhinal neurons signal both flexible associative memory and recall.

Associative learning and memory signals in the perirhinal cortex have typically been studied using a visual-visual pair-association (VPA) task (Sakai & Miyashita 1991; Erickson & Desimone 1999; Messinger et al. 2001; Naya et al. 2003a,b). In this task, a visual object is presented as a cue stimulus, and after a delay period, a monkey is required to choose a unique, geometrically unrelated visual object that has been paired in memory with the cue stimulus. The perirhinal cortex contains many pair-coding neurons (33% of stimulus-selective neurons) that show significantly ($p < 0.01$) correlated responses to the two visual stimuli in a particular learned pair (Naya et al. 2003a). These striking neurophysiological results are consistent with findings from lesion studies showing that bilateral damage to the perirhinal cortex results in impairment of visual-visual associative memory (Murray et al. 1993, Buckley & Gaffan 1998). Relative to the perirhinal cortex, substantially fewer (4.9%) pair-coding neurons were observed in visual area TE (Naya et al. 2003a). We do not know whether pair-coding perirhinal neurons are generated by converging inputs from individual TE neurons that code the individual stimuli that constitute the paired associate (selective-convergence model) or if they are generated by direct inputs from individual (though sparse) pair-coding neurons in TE (direct-driven model) (Naya et al. 2003a, Hirabayashi et al. 2013b). In either case, the interactions between the perirhinal cortex and area TE are important for item-item association memory (Yoshida et al. 2003). A recent study suggests that pair-coding neurons in area TE are generated by their intrinsic microcircuits (Hirabayashi et al. 2013b). Results from lesion studies in monkeys further suggest that these microcircuits in area TE are influenced by feedback projections from the perirhinal and entorhinal cortices (Higuchi & Miyashita 1996).

Dual-process models allow for an associative function of the perirhinal cortex but suggest that it provides a less flexible unitized kind of associative signal (Davachi 2006, Diana et al. 2007). Although the idea of a unitized representation in the perirhinal cortex is consistent with the description of pair-coding neurons as having a correlated (i.e., similar or unitized) neural response to the two visual stimuli that have been associated in memory (Sakai & Miyashita 1991, Naya et al. 2003a), a more detailed examination of the neurophysiological data suggests a more complex

reality. First, despite the fact that perirhinal pair-coding signals show correlated responses to particular learned paired associates, neurons in areas 35 and 36 nonetheless maintain differential response amplitudes to the two different stimuli in the associated pair during the cue presentation period (Fujimichi et al. 2010). This finding suggests that the responses of the perirhinal neurons to the visual stimuli themselves, although significantly correlated, remain distinct and ununitized. However, the story differs for activity during the delay period immediately following the cue presentation. During the delay period of the task, neurons in area 35 (the small subdivision of the perirhinal cortex) represent paired items indiscriminately (i.e., in a unitized fashion), whereas neurons in area 36 (the larger perirhinal subdivision) continue to maintain distinct representations of the associated stimuli. Thus while the entire perirhinal cortex maintains distinct representation of the paired stimuli during the cue presentation period and the largest subdivision (area 36) also maintains this differential response during the delay period, the smaller perirhinal subdivision (area 35) exhibits a clear unitized representation only during the delay period.

Another striking example of associative flexibility in the perirhinal cortex is a unique activity pattern seen during the delay interval of the VPA task. During this period, pair-recall neurons signal the identity of the to-be-remembered paired associate (Sakai & Miyashita 1991; Naya et al. 1996, 2003b), and this neural response represents one of the most striking examples of a long-term associative recall signal ever reported. A subsequent study showed that this recall signal appeared first in area 36 and was propagated backward to area TE, where it was observed at longer latencies (Naya et al. 2001). This physiological finding is consistent with the extensive back projections from area 36 to TE (see The Anatomy of the Perirhinal Cortex, above). Thus, the perirhinal cortex not only signals a long-term representation of the learned paired associates during the cue period of the task (pair-coding neurons), but also provides a highly flexible recollection signal of the sought target during the delay period immediately preceding the choice period of the task (pair-recall neurons).

An important question concerns how the memory retrieval signal develops in the perirhinal cortex. One study showed that area 36 pair-recall signals start as early as the cue period of the VPA task (Naya et al. 2001). However, this study did not directly examine the relationship between these early-responding pair-recall neurons and the pair-coding neurons during the cue period of the task (Naya & Suzuki 2010). One recent study using simultaneous multiunits recording in area 36 used causality analysis to examine the circuits involved in recall during the delay period of the VPA task (Hirabayashi et al. 2013a). This study focused on the relationship between the pair-recall neurons and another category of neurons in the perirhinal cortex known as cue-holding neurons. Cue-holding neurons maintain a representation of a preferred cue stimulus after stimulus offset during the subsequent delay period, which can be considered a form of persistence memory (Naya et al. 2003b). Granger causality analyses suggested a direct coupling from the cue-holding neurons to the pair-recall neurons during the delay period of the VPA task. This result implies that the retrieval of item-item association memory during the delay period may take place through a signal cascade from the cue-holding neurons to the pair-recall neurons. Thus, the perirhinal cortex is deeply involved in the recall/recollection process, and these data are inconsistent with many versions of dual-process models that clearly place recall/recollection functions exclusively in the domain of the hippocampus (Diana et al. 2007, Eichenbaum et al. 2007). It is important to note that no parallel studies of monkey physiology during the VPA task have compared the responses between the perirhinal cortex and hippocampus or examined the interactions between these regions. These kinds of studies will be important to determine, for example, if these regions provide a complementary or a distinct recall/recollection signal during VPA tasks. Other studies described below, however, have directly compared hippocampal and perirhinal neural responses on the same associative learning or memory task.

Between-domain associations. One dual-process model suggests that the perirhinal cortex conveys information for unitized associations and for nonunitized within-domain associations (Mayes et al. 2007). However, this assumption is inconsistent with its convergent projections not only from visual association areas (area TE), but also from areas involved in signaling contextual (hippocampal formation/parahippocampal cortex), spatial (hippocampal formation/parahippocampal cortex), and reward (orbitofrontal cortex) information. For example, perirhinal neural responses have been studied during a conditional motor associative learning task in which animals were required to associate a complex visual scene with a particular rewarded target location (Wirth et al. 2003). This task is also referred to as a location-scene association task and is sensitive to damage to the hippocampus (Gaffan 1992, Murray & Wise 1996) and the perirhinal cortex (Murray et al. 1998). In this task, animals are presented with a complex visual scene with four identical target locations superimposed on it. After a delay interval during which the scene disappears but the four target locations remain visible on the screen, the animal is cued to make an eye movement to a target location, only one of which is rewarded for any given visual scene. With trial and error, animals learn between 2 and 4 novel location-scene associations each session. Yanike et al. (2009) described perirhinal "changing cells" that either came to respond selectively or lost their selective response. This changing neural activity was strongly correlated with the animal's behavioral learning curve for that particular association. Direct and detailed comparison of the timing of the changing cells relative to learning in the hippocampus and the perirhinal cortex suggested that the timing of the changing cells was not different between these two areas (Yanike et al. 2009). Consistent with these findings in monkeys, a parallel study in humans performing a very similar conditional motor association learning task confirmed similar patterns of changing activity in the hippocampus and perirhinal cortex correlated with behavioral performance (Law et al. 2005). These findings show that the perirhinal cortex can signal conjunctions of complex visual stimuli and learned target locations, and they suggest that for new conditional motor associative learning the perirhinal cortex and hippocampus act in parallel to signal the formation of new associations in memory in both monkeys and humans.

Perirhinal and hippocampal responses have also been characterized during the performance of a temporal order memory task. During an encoding phase, animals were shown a sequence of two unique visual items. During a subsequent retrieval phase, these same two items and one distracter stimulus were shown in pseudorandom locations on a video monitor, and the animals were required to touch the first-presented item and then the second (avoiding a distractor image) to obtain a juice reward. Not only did perirhinal neurons provide a prominent visually selective response, but this response was significantly modulated by the temporal order of the stimulus presentation (Naya & Suzuki 2011). Unlike for the conditional motor association task, described above, the hippocampus did not provide a similar item-time association. Instead, a prominent incremental timing signal was seen during the delay period between two item presentations (Pastalkova et al. 2008, MacDonald et al. 2011, Naya & Suzuki 2011). These two examples taken together not only show that perirhinal neurons signal a range of between-domain associations, but also suggest that the perirhinal cortex and hippocampus can respond either very similarly or in distinct ways depending on the particular task demands (i.e., associative learning versus temporal order memory).

Another between-domain association that has been explored in the perirhinal cortex is object-reward associations (Liu et al. 2000, Liu & Richmond 2000, Mogami & Tanaka 2006, Ohyama et al. 2012). Perirhinal neurons can represent the association between particular visual stimuli and particular reward outcomes (Mogami & Tanaka 2006) or cues signaling the imminent arrival of reward (Liu et al. 2000, Liu & Richmond 2000). One recent study reported that perirhinal neurons represent reward information predicted by a configuration of two visual objects (Ohyama et al. 2012). In this task, two visual stimuli are presented sequentially such that the configuration

of two cue stimuli predicted upcoming reward. During the second stimulus presentation, substantial numbers of perirhinal neurons showed activity selective to the predicted reward condition regardless of the identity of the second cue stimulus. These findings suggest that the perirhinal cortex signals item-reward associations and can provide a flexible representation for expected reward. Determining which brain region(s) interact with the perirhinal cortex to process information about reward is important. Using a crossed unilateral lesion of the orbitofrontal cortex on one side and the perirhinal and entorhinal cortices on the other, Clark et al. (2013) showed that perirhinal/entorhinal interactions with the orbitofrontal cortex, an area strongly associated with signaling the features of reward (de Araujo et al. 2003, Padoa-Schioppa & Assad 2006, Chaudhry et al. 2009), are essential for monkeys to distinguish between different reward sizes. These findings support the idea that reward information from the orbitofrontal cortex may be combined with associative and contextual information in the perirhinal and entorhinal cortices to estimate expected value.

As highlighted in the anatomy section above, one of the most prominent projections to the perirhinal cortex comes from the adjacent entorhinal and parahippocampal cortices, which both signal aspects of contextual/spatial memory (Hargreaves et al. 2005, Aminoff et al. 2007, Bar et al. 2008). Although dual-process theories typically limit contextual processing to the hippocampus and the parahippocampal cortex, a growing body of reports from fMRI studies have described object-context associations in the perirhinal cortex (Smith et al. 1981, Staresina & Davachi 2008, Staresina et al. 2011), in some cases, similar to contextual associations signaled by the hippocampus, and in other cases, distinct from hippocampal signals. One study scanned subjects as they encoded visual items associated with one of two different contexts (e.g., common versus uncommon items or curved versus straight items) (Watson et al. 2012). Perirhinal activity predicted the accuracy of the retrieval judgments about the behavioral context during the encoding period, and this finding was maintained when memory strength was equated across the items. Thus, even contextual associations, a function typically considered strictly in the domain of the hippocampus in most dual-process models is represented in the perirhinal cortex.

Perirhinal-Amygdala Interactions

A growing body of work has been exploring the functional role of the prominent interconnections between the perirhinal cortex and the amygdala. One study demonstrated simultaneous recording of the perirhinal cortex, the entorhinal cortex, and the basolateral amygdala (BLA) during a trace-conditioning task (Paz et al. 2006). They reported that early in the learning process, BLA activity was associated with increased signal transmission from the perirhinal cortex to the entorhinal cortex, and this activity was increased markedly after reward delivery. Previous studies reported strong inhibition in the projection from the perirhinal cortex to the entorhinal cortex (de Curtis & Pare 2004). In this way, the perirhinal cortex appears to serve as an active gateway of information flow from neocortical areas toward the hippocampus, which can be modulated by the emotional salience of the present situation (Fernandez & Tendolkar 2006, Paz & Pare 2013).

Recent studies show that lesions of rat perirhinal cortex also impaired a range of fear-conditioning paradigms, including trace and delay conditioning (Kent & Brown 2012). Kent & Brown (2012) suggest two ways that the perirhinal cortex may contribute to conditioning. They suggest first that the perirhinal cortex is essential for bridging the temporal gap in the trace-conditioning paradigms because of the prominent persistent activity that has been shown in perirhinal slice preparations, known as endogenous persistent firing (EPF). EPF was first described in entorhinal slice preparations (Egorov et al. 2002, Fransén et al. 2006) and is characterized by persistent neural spiking activity that continues long after the termination of the spike-eliciting

current (Navaroli et al. 2012). In fact, this striking cellular phenomenon in the perirhinal cortex is consistent with many other reports of striking perirhinal delay activity. Examples include the recall and cue holding signals seen in the VPA task described above (Naya et al. 2003b), as well as the persistent delay activity seen during a delayed match-to-sample task (Schon et al. 2005), and in situations where implicit learning between temporally adjacent items takes place (Miyashita 1988, Yakovlev et al. 1998, Schapiro et al. 2012). These findings suggest that the perirhinal cortex provides a wide range of transient/persistent memory signals, some of which serve trace conditioning.

Kent & Brown (2012) argue that the perirhinal cortex, in addition to its role in transient memory for the trace interval, contributes to the performance of certain conditioning tasks because of its role in processing particular kinds of conditional stimuli (CS). They argue that the perirhinal cortex is critical when processing CS requiring the ability to treat two or more items or elements as a single entity. Examples of CS requiring an intact perirhinal cortex in rodents include ultrasonic vocalizations, spatial contexts, and discontinuous auditory "pips." Kent & Brown (2012) link this interpretation to theories that emphasize the perceptual functions of the perirhinal cortex (Murray & Wise 2012). However, as we argue below, the data used to support this theory can be interpreted in more than one way.

Perception Although the perirhinal cortex has often been considered to work predominantly for declarative memory (Squire et al. 2007, Wixted & Squire 2010), strong evidence shows that lesions to the perirhinal cortex also impair performances on tasks designed to tap perceptual functions (Buckley et al. 2001, Bussey & Saksida 2007, Graham et al. 2010; but see Shrager et al. 2006). Tasks that show impairment with perirhinal lesions typically cannot be solved on the basis of single feature comparisons. Instead, tasks that show impairment require subjects to choose an odd stimulus out of concurrently presented complex objects or to discriminate between complex objects that contain multiple overlapping elements. These findings suggest that the perirhinal cortex is important for perceptual discriminations when high feature ambiguity is present. These findings also form the basis for a theory that we refer to as the perirhinal perceptual model (PPM), which states that the perirhinal cortex is a perceptual area important for both perception and memory (Bussey et al. 2005, Murray & Wise 2012).

The question of whether the perirhinal cortex should be considered primarily a memory area or an area that participates in both perception and memory has been addressed and debated previously in the literature (Hampton 2005, Baxter 2009, Suzuki 2009b, Suzuki & Baxter 2009, Murray & Wise 2012). The new insight we bring to this debate comes from a detailed consideration of the unique neurophysiological properties of the perirhinal cortex. These unique physiological properties have direct relevance for interpreting the deficit seen on concurrent and oddity discrimination tasks following perirhinal lesions. To solve these tasks successfully, multiple complex stimulus elements must be quickly bound together and then held in memory as they are compared with the other exemplars with multiple overlapping elements. According to the PPM model, the perirhinal cortex solves this problem by encoding conjunctions between sensory features that serve perception (Bussey et al. 2005). The data from the physiological evidence reviewed above suggest that these conjunctions/associations can be encoded by the prominent within-domain (Naya et al. 2003a) and between-domain (Yanike et al. 2009, Naya & Suzuki 2011, Ohyama et al. 2012) associative functions of the perirhinal cortex. It is the broad set of associative memory functions that engage the perirhinal cortex in this particular subset of perceptual tasks that are impaired by perirhinal lesions.

Moreover, once these conjunctive stimuli are represented, they must be maintained in memory during the comparison process. Other physiological evidence described above shows that the

perirhinal cortex can represent multiple items through the delay period (Naya et al. 2003b) and can signal the identity of previously presented information over both short and long timescales (Yakovlev et al. 1998, Naya et al. 2003b, Schon et al. 2004). This form of persistent memory may be helpful particularly in situations where large complex amounts of visual information must be held in mind for comparison across visual objects. Thus, we suggest that the impairment seen following perirhinal damage on certain oddity or concurrent discrimination tasks may not be due to perirhinal perceptual functions, but instead to its prominent and diverse mnemonic properties (**Table 1**). How can we definitively distinguish between these two possibilities? We suggest that it will be important to record during oddity or concurrent discrimination as well as during other clear memory-demanding tasks to determine if the perirhinal cortex provides similar mnemonic signals across both categories of tasks (Suzuki 2009b).

SUMMARY

This review shows that the perirhinal cortex is truly a multifaceted memory area that can convey information about stimulus familiarity, within- and between-domain associative learning, memory, and recall and can synergize with the amygdala to modulate information flow to the hippocampus relative to the emotional salience of the situation (**Table 1**). We argue that these mnemonic signals serve declarative memory. Moreover, we argue that the associative learning signals together with persistent delay activity present in this area may underlie the striking deficits seen on oddity and concurrent discrimination tasks, which were previously interpreted as perceptual deficits.

When comparing the diverse mnemonic functions of the perirhinal cortex with those of the hippocampus, neurophysiological studies show that depending on the task demands, investigators see both clear dissociations between the different MTL areas (i.e., temporal order memory task) consistent with dual-process models as well as striking similarities in the signals conveyed by these areas (location-scene association task) consistent with single-process models. This wide range of neurophysiological findings parallel the conflicting pattern of findings cited by the single process and dual process models and suggest that, depending on the situation, both patterns can be seen (Eichenbaum et al. 2007, Wixted & Squire 2010). To address these conflicting models in one comprehensive framework, we suggest a conditionally dynamic model (CD model) of MTL function. This model states that depending on the present task, different MTL structures can express either similar or distinct/dissociable memory signals. Specific task demands as well as the functional interactions between these areas are two key factors that will determine if these structures convey similar or distinct/dissociable signals. An important goal for future studies will be to determine both when and how the interactions between these MTL structures result in either similar or distinct patterns of activity.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

LITERATURE CITED

Aggleton JP, Brown MW, Albasser MM. 2012. Contrasting brain activity patterns for item recognition memory and associative recognition memory: insights from immediate-early gene functional imaging. *Neuropsychologia* 50(13):3141–55

Aminoff E, Gronau N, Bar M. 2007. The parahippocampal cortex mediates spatial and nonspatial associations. *Cereb. Cortex* 17(7):1493–503

Bar M, Aminoff E, Ishai A. 2008. Famous faces activate contextual associations in the parahippocampal cortex. *Cereb. Cortex* 18(6):1233–38

Baxter MG. 2009. Involvement of medial temporal lobe structures in memory and perception. *Neuron* 61(5):667–77

Brodmann K. 1909. *Vergleichende Lokalisationslehre der Grosshirnrinde*. Leipzig: Johann Ambrosius Barth

Brown MW, Aggleton JP. 2001. Recognition memory: What are the roles of the perirhinal cortex and hippocampus? *Nat. Rev. Neurosci.* 2(1):51–61

Brown MW, Warburton EC, Aggleton JP. 2010. Recognition memory: material, processes, and substrates. *Hippocampus* 20(11):1228–44

Buckley MJ, Booth MCA, Rolls ET, Gaffan D. 2001. Selective perceptual impairments after perirhinal cortex ablation. *J. Neurosci.* 21(24):9824–36

Buckley MJ, Gaffan D. 1998. Perirhinal cortex ablation impairs visual object identification. *J. Neurosci.* 18(6):2268–75

Burwell RD, Amaral DG. 1998. Perirhinal and postrhinal cortices of the rat: interconnectivity and connections with the entorhinal cortex. *J. Comp. Neurol.* 391(3):293–321

Bussey TJ, Saksida LM. 2007. Memory, perception, and the ventral visual-perirhinal-hippocampal stream: thinking outside of the boxes. *Hippocampus* 17(9):898–908

Bussey TJ, Saksida LM, Murray EA. 2005. The perceptual-mnemonic/feature conjunction model of perirhinal cortex function. *Q. J. Exp. Psychol. B* 58(3–4):269–82

Chaudhry AM, Parkinson JA, Hinton EC, Owen AM, Roberts AC. 2009. Preference judgements involve a network of structures within frontal, cingulate and insula cortices. *Eur. J. Neurosci.* 29(5):1047–55

Clark AM, Bouret S, Young AM, Murray EA, Richmond BJ. 2013. Interaction between orbital prefrontal and rhinal cortex is required for normal estimates of expected value. *J. Neurosci.* 33(5):1833–45

Davachi L. 2006. Item, context and relational episodic encoding in humans. *Curr. Opin. Neurobiol.* 16(6):693–700

de Araujo IE, Rolls ET, Kringelbach ML, McGlone F, Phillips N. 2003. Taste-olfactory convergence, and the representation of the pleasantness of flavour, in the human brain. *Eur. J. Neurosci.* 18(7):2059–68

de Curtis M, Paré D. 2004. The rhinal cortices: a wall of inhibition between the neocortex and the hippocampus. *Prog. Neurobiol.* 74(2):101–10

Diana RA, Yonelinas AP, Ranganath C. 2007. Imaging recollection and familiarity in the medial temporal lobe: a three-component model. *Trends Cogn. Sci.* 11(9):379–86

Egorov AV, Hamam BN, Fransén E, Hasselmo ME, Alonso AA. 2002. Graded persistent activity in entorhinal cortex neurons. *Nature* 420:173–78

Eichenbaum H, Cohen NJ. 2001. *From Conditioning to Conscious Recollection*. New York: Oxford Univ. Press

Eichenbaum H, Yonelinas AR, Ranganath C. 2007. The medial temporal lobe and recognition memory. *Annu. Rev. Neurosci.* 30:123–52

Erickson CA, Desimone R. 1999. Responses of macaque perirhinal neurons during and after visual stimulus association learning. *J. Neurosci.* 19(23):10404–16

Fernandez G, Tendolkar I. 2006. The rhinal cortex: 'gatekeeper' of the declarative memory system. *Trends Cogn. Sci.* 10(8):358–62

Foster DJ, Wilson MA. 2006. Reverse replay of behavioural sequences in hippocampal place cells during the awake state. *Nature* 440(7084):680–83

Fransén E, Tahvildari B, Egorov AV, Hasselmo ME, Alonso AA. 2006. Mechanism of graded persistent cellular activity of entorhinal cortex layer V neurons. *Neuron* 49(5):735–46

Fujimichi R, Naya Y, Koyano KW, Takeda M, Takeuchi D, Miyashita Y. 2010. Unitized representation of paired objects in area 35 of the macaque perirhinal cortex. *Eur. J. Neurosci.* 32(4):659–67

Gaffan D. 1992. Amnesia for complex naturalistic scenes and for objects following fornix transection in the rhesus monkey. *Eur. J. Neurosci.* 4:381–88

Graham KS, Barense MD, Lee AC. 2010. Going beyond LTM in the MTL: a synthesis of neuropsychological and neuroimaging findings on the role of the medial temporal lobe in memory and perception. *Neuropsychologia* 48(4):831–53

Hampton RR. 2005. Monkey perirhinal cortex is critical for visual memory, but not for visual perception: reexamination of the behavioural evidence from monkeys. *Q. J. Exp. Psychol. B* 58(3–4):283–99

Hargreaves EL, Rao G, Lee I, Knierim JJ. 2005. Major dissociation between medial and lateral entorhinal input to dorsal hippocampus. *Science* 308:1792–94

Higuchi S-I, Miyashita Y. 1996. Neural code of visual paired associate memory in primate inferotemporal cortex is impaired by perirhinal and entorhinal lesions. *Proc. Natl. Acad. Sci. USA* 93:739–43

Hirabayashi T, Takeuchi D, Tamura K, Miyashita Y. 2013a. Functional microcircuit recruited during retrieval of object association memory in monkey perirhinal cortex. *Neuron* 77(1):192–203

Hirabayashi T, Takeuchi D, Tamura K, Miyashita Y. 2013b. Microcircuits for hierarchical elaboration of object coding across primate temporal areas. *Science* 341:191–95

Insausti R, Amaral DG, Cowan WM. 1987. The entorhinal cortex of the monkey: II. Cortical afferents. *J. Comp. Neurol.* 264:356–95

Insausti R, Muñoz M. 2001. Cortical projections of the non-entorhinal hippocampal formation in the cynomolgus monkey (*Macaca fascicularis*). *Eur. J. Neurosci.* 14(3):435–51

Jones EG, Powell TPS. 1970. An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain* 93:793–820

Kent BA, Brown TH. 2012. Dual functions of perirhinal cortex in fear conditioning. *Hippocampus* 22(10):2068–79

Kuhl BA, Rissman J, Chun MM, Wagner AD. 2011. Fidelity of neural reactivation reveals competition between memories. *Proc. Natl. Acad. Sci. USA* 108(14):5903–8

Lavenex P, Suzuki WA, Amaral DG. 2002. Perirhinal and parahippocampal cortices of the macaque monkey: projections to the neocortex. *J. Comp. Neurol.* 447(4):394–420

Lavenex P, Suzuki WA, Amaral DG. 2004. Perirhinal and parahippocampal cortices of the macaque monkey: intrinsic projections and interconnections. *J. Comp. Neurol.* 472(3):371–94

Law JR, Flanery MA, Wirth S, Yanike M, Smith AC, et al. 2005. Functional magnetic resonance imaging activity during the gradual acquisition and expression of paired-associate memory. *J. Neurosci.* 25(24):5720–29

Liu Z, Murray EA, Richmond BJ. 2000. Learning motivational significance of visual cues for reward schedules requires rhinal cortex. *Nat. Neurosci.* 3(12):1307–15

Liu Z, Richmond BJ. 2000. Response differences in monkey TE and perirhinal cortex: stimulus association related to reward schedules. *J. Neurophysiol.* 83(3):1677–92

MacDonald CJ, Legage KQ, Eden UT, Eichenbaum H. 2011. Hippocampal "time cells" bridge the gap in memory for discontiguous events. *Neuron* 71(4):737–49

Mayes A, Montaldi D, Migo E. 2007. Associative memory and the medial temporal lobes. *Trends Cogn. Sci.* 11(3):126–35

Messinger A, Squire LR, Zola SM, Albright TD. 2001. Neuronal representations of stimulus associations develop in the temporal lobe during learning. *Proc. Natl. Acad. Sci.* 98(21):12239–44

Miyashita Y. 1988. Neuronal correlate of visual associative long-term memory in the primate temporal cortex. *Nature* 335:817–20

Mogami T, Tanaka K. 2006. Reward association affects neuronal responses to visual stimuli in macaque TE and perirhinal cortices. *J. Neurosci.* 26(25):6761–70

Mohedano-Moriano A, Martinez-Marcos A, Pro-Sistiaga P, Blaizot X, Arroyo-Jimenez MM, et al. 2008. Convergence of unimodal and polymodal sensory input to the entorhinal cortex in the fascicularis monkey. *Neuroscience* 151(1):255–71

Muñoz M, Insausti R. 2005. Cortical efferents of the entorhinal cortex and the adjacent parahippocampal region in the monkey (*Macaca fascicularis*). *Eur. J. Neurosci.* 22(6):1368–88

Murray EA, Bachevalier J, Mishkin M. 1989. Effects of rhinal cortical lesions on visual recognition memory in rhesus monkeys. *Soc. Neurosci. Abstr.* 15:342 (Abstr.)

Murray EA, Baxter MG, Gaffan D. 1998. Monkeys with rhinal cortex damage or neurotoxic hippocampal lesions are impaired on spatial scene learning and object reversals. *Behav. Neurosci.* 112:1291–303

Murray EA, Gaffan D, Mishkin M. 1993. Neural substrates of visual stimulus-stimulus association in rhesus monkeys. *J. Neurosci.* 13:4549–61

Murray EA, Richmond BJ. 2001. Role of perirhinal cortex in object perception, memory, and associations. *Curr. Opin. Neurobiol.* 11(2):188–93

Murray EA, Wise SP. 1996. Role of the hippocampus plus subjacent cortex but not amygdala in visuomotor conditional learning in rhesus monkeys. *Behav. Neurosci.* 110(6):1261–70

Murray EA, Wise SP. 2012. Why is there a special issue on perirhinal cortex in a journal called *Hippocampus*? The perirhinal cortex in historical perspective. *Hippocampus* 22(10):1941–51

Navaroli VL, Zhao Y, Boguszewski P, Brown TH. 2012. Muscarinic receptor activation enables persistent firing in pyramidal neurons from superficial layers of dorsal perirhinal cortex. *Hippocampus* 22(6):1392–404

Naya Y, Sakai K, Miyashita Y. 1996. Activity of primate inferotemporal neurons related to a sought target in pair-association task. *Proc. Natl. Acad. Sci. USA* 93(7):2664–69

Naya Y, Suzuki WA. 2010. Associative memory in the medial temporal lobe. In *Primate Neuroethology*, ed. M Platt, A Ghazanfar, pp. 337–58. Oxford, UK: Oxford Univ. Press

Naya Y, Suzuki WA. 2011. Integrating what and when across the primate medial temporal lobe. *Science* 333:773–76

Naya Y, Yoshida M, Miyashita Y. 2001. Backward spreading of memory-retrieval signal in the primate temporal cortex. *Science* 291:661–64

Naya Y, Yoshida M, Miyashita Y. 2003a. Forward processing of long-term associative memory in monkey inferotemporal cortex. *J. Neurosci.* 23(7):2861–71

Naya Y, Yoshida M, Takeda M, Fujimichi R, Miyashita Y. 2003b. Delay-period activities in two subdivisions of monkey inferotemporal cortex during pair association memory task. *Eur. J. Neurosci.* 18(10):2915–18

Ohyama K, Sugase-Miyamoto Y, Matsumoto N, Shidara M, Sato C. 2012. Stimulus-related activity during conditional associations in monkey perirhinal cortex neurons depends on upcoming reward outcome. *J. Neurosci.* 32(48):17407–19

Padoa-Schioppa C, Assad JA. 2006. Neurons in the orbitofrontal cortex encode economic value. *Nature* 441:223–26

Pastalkova E, Itskov V, Amarasingham A, Buzsáki G. 2008. Internally generated cell assembly sequences in the rat hippocampus. *Science* 321:1322–27

Paz R, Pare D. 2013. Physiological basis for emotional modulation of memory circuits by the amygdala. *Curr. Opin. Neurobiol.* 23(3):381–86

Paz R, Pelletier JG, Bauer EP, Paré D. 2006. Emotional enhancement of memory via amygdala-driven facilitation of rhinal interactions. *Nat. Neurosci.* 9(10):1321–29

Polyn SM, Natu VS, Cohen JD, Norman KA. 2005. Category-specific cortical activity precedes retrieval during memory search. *Science* 310:1963–66

Ranganath C, Ritchey M. 2012. Two cortical systems for memory-guided behaviour. *Nat. Rev. Neurosci.* 13(10):713–26

Sakai K, Miyashita Y. 1991. Neural organization for the long-term memory of paired associates. *Nature* 354:152–55

Schapiro AC, Kustner LV, Turk-Browne NB. 2012. Shaping of object representations in the human medial temporal lobe based on temporal regularities. *Curr. Biol.* 22(17):1622–27

Schon K, Atri A, Hasselmo ME, Tricarico MD, Lopresti ML, Stern CE. 2005. Scopolamine reduces persistent activity related to long-term encoding in the parahippocampal gyrus during delayed matching in humans. *J. Neurosci.* 25(40):9112–23

Schon K, Hasselmo ME, Lopresti ML, Tricarico MD, Stern CE. 2004. Persistence of parahippocampal representation in the absence of stimulus input enhances long-term encoding: a functional magnetic resonance imaging study of subsequent memory after a delayed match-to-sample task. *J. Neurosci.* 24(49):11088–97

Shrager Y, Gold JJ, Hopkins RO, Squire LR. 2006. Intact visual perception in memory-impaired patients with medial temporal lobe lesions. *J. Neurosci.* 26(8):2235–40

Smith EL III, Harwerth RS, Levi DM, Watson JT. 1981. Normal cortical responses in ocularly hypopigmented cats. *Brain Res.* 206:183–86

Squire LR, Wixted JT, Clark RE. 2007. Recognition memory and the medial temporal lobe: a new perspective. *Nat. Rev. Neurosci.* 8:872–83

Staresina BP, Davachi L. 2008. Selective and shared contributions of the hippocampus and perirhinal cortex to episodic item and associative encoding. *J. Cogn. Neurosci.* 20(8):1478–89

Staresina BP, Davachi L. 2009. Mind the gap: binding experiences across space and time in the human hippocampus. *Neuron* 63(2):267–76

Staresina BP, Duncan KD, Davachi L. 2011. Perirhinal and parahippocampal cortices differentially contribute to later recollection of object- and scene-related event details. *J. Neurosci.* 31(24):8739–47

Stefanacci L, Suzuki WA, Amaral DG. 1996. Organization of connections between the amygdaloid complex and the perirhinal and parahippocampal cortices in macaque monkeys. *J. Comp. Neurol.* 375:552–82

Suzuki WA. 2009a. Comparative analysis of the cortical afferents, intrinsic projections and interconnections of the parahippocampal regions in monkeys and rats. In *The Cognitive Neurosciences*, ed. M Gazzaniga, pp. 659–74. Boston, MA: MIT Press

Suzuki WA. 2009b. Perception and the medial temporal lobe: evaluating the current evidence. *Neuron* 61(5):657–66

Suzuki WA, Amaral DG. 1990. Cortical inputs to the CA1 field of the monkey hippocampus originate from the perirhinal and parahippocampal cortex but not from area TE. *Neurosci. Lett.* 115:43–48

Suzuki WA, Amaral DG. 1994a. Perirhinal and parahippocampal cortices of the macaque monkey: cortical afferents. *J. Comp. Neurol.* 350:497–533

Suzuki WA, Amaral DG. 1994b. Topographic organization of the reciprocal connections between monkey entorhinal cortex and the perirhinal and parahippocampal cortices. *J. Neurosci.* 14:1856–77

Suzuki WA, Amaral DG. 2003. The perirhinal and parahippocampal cortices of the macaque monkey: cytoarchitectonic and chemoarchitectonic organization. *J. Comp. Neurol.* 463:67–91

Suzuki WA, Baxter MG. 2009. Memory, perception, and the medial temporal lobe: a synthesis of opinions. *Neuron* 61(5):678–79

Suzuki WA, Zola-Morgan S, Squire LR, Amaral DG. 1993. Lesions of the perirhinal and parahippocampal cortices in the monkey produce long-lasting memory impairment in the visual and tactual modalities. *J. Neurosci.* 13:2430–51

Van Hoesen GW, Pandya DN. 1975. Some connections of the entorhinal (area 28) and perirhinal (area 35) cortices of the rhesus monkey. I. Temporal lobe afferents. *Brain Res.* 95:1–24

Watson HC, Wilding EL, Graham KS. 2012. A role for perirhinal cortex in memory for novel object-context associations. *J. Neurosci.* 32(13):4473–81

Wirth S, Yanike M, Frank LM, Smith AC, Brown EN, Suzuki WA. 2003. Single neurons in the monkey hippocampus and learning of new associations. *Science* 300:1578–81

Wixted JT, Squire LR. 2010. The role of the human hippocampus in familiarity-based and recollection-based recognition memory. *Behav. Brain Res.* 215(2):197–208

Xiang JZ, Brown MW. 1998. Differential neuronal encoding of novelty, familiarity and recency in regions of the anterior temporal lobe. *Neuropharmacology* 37:657–76

Yakovlev V, Fusi S, Berman E, Zohary E. 1998. Inter-trial neuronal activity in inferior temporal cortex: a putative vehicle to generate long-term visual associations. *Nat. Neurosci.* 1(4):310–17

Yanike M, Wirth S, Smith AC, Brown EN, Suzuki WA. 2009. Comparison of associative learning-related signals in the macaque perirhinal cortex and hippocampus. *Cereb. Cortex* 19(5):1064–78

Yoshida M, Naya Y, Miyashita Y. 2003. Anatomical organization of forward fiber projections from area TE to perirhinal neurons representing visual long-term memory in monkeys. *Proc. Natl. Acad. Sci. USA* 100(7):4257–62

Yukie M. 2000. Connections between the medial temporal cortex and the CA1 subfield of the hippocampal formation in the Japanese monkey (*Macaca fuscata*). *J. Comp. Neurol.* 423:282–98

Zola-Morgan S, Squire LR, Amaral DG, Suzuki WA. 1989. Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. *J. Neurosci.* 9:4355–70

Contents

Indexes

Errata

An online log of corrections to *Annual Review of Neuroscience* articles may be found at http://www.annualreviews.org/errata/neuro

ANNUAL REVIEWS

It's about time. Your time. It's time well spent.

New From Annual Reviews:

Annual Review of Statistics and Its Application

Volume 1 • Online January 2014 • http://statistics.annualreviews.org

Editor: **Stephen E. Fienberg,** *Carnegie Mellon University*

Associate Editors: **Nancy Reid,** *University of Toronto*

Stephen M. Stigler, *University of Chicago*

The *Annual Review of Statistics and Its Application* aims to inform statisticians and quantitative methodologists, as well as all scientists and users of statistics about major methodological advances and the computational tools that allow for their implementation. It will include developments in the field of statistics, including theoretical statistical underpinnings of new methodology, as well as developments in specific application domains such as biostatistics and bioinformatics, economics, machine learning, psychology, sociology, and aspects of the physical sciences.

Complimentary online access to the first volume will be available until January 2015.

Access this and all other Annual Reviews journals via your institution at www.annualreviews.org.