EXPERIENCE-DEPENDENT NETWORK MODIFICATION IN THE MEDIAL TEMPORAL LOBE

by

Alexander Thome

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ABSTRACT

Theoretical models of information storage in the brain have suggested that neurons may undergo an experience-dependent tuning or sharpening of their representations in order to maximize the amount of information that can be stored. Changes in the tuning profiles of neurons have been demonstrated to occur when animals must learn perceptual discriminations, however, whether similar changes occur in the absence of behavioral demands is unclear. To address these questions, the activity of simultaneously recorded medial temporal lobe (MTL) neurons was studied in relation to a passive visual recognition memory task. The structure of this task was such that it allowed for a comparison between novelty related responses as well as tuning properties of individual neurons. A total of 565 well isolated single neurons were recorded from four rhesus macaques. The first contribution of this dissertation is the finding of a dissociation between different medial temporal lobe regions such that neurons in temporal area F (**TF**), but not perirhinal cortex (**PRC**) or the hippocampus, show an experience-dependent change in their stimulus selectivity. This finding indicates that tuning of stimulus representations may be an effective mechanism for maximizing information storage in some brain regions. The absence of stimulus tuning in higher level association regions (i.e. TF and PRC) suggests that tuning in these regions may be disadvantageous due to the need to construct unified representations across sensory modalities. A complimentary question to the question of network storage capacity is how networks avoid saturation in the connections between neurons. The

second contribution of this dissertation is the finding that there exists a decrease in the magnitude of the short time scale correlations between pairs of neurons; suggesting that networks reduce the number of connections between neurons as a stimulus becomes familiar. Gamma oscillations have been proposed to be the mechanism by which groups of neurons coordinate their activity. However, network coordination has only been indirectly measured. The final contribution of this dissertation is the finding that the magnitude of gamma oscillations is strongly correlated with enhanced magnitude of correlations between neurons.

CHAPTER 1 - INTRODUCTION - MEMORY AND NEURAL CODES

The average person will encounter a vast sea of objects over the course of its life, each of which carries with it unique physical attributes. Strikingly, we can recall perfectly the specific episode (i.e., time and place) in which we encountered an object. A central question for neuroscience has been to understand how the brain manages to accurately—and more importantly, efficiently—store this vast amount of information. Approached from the organismic level, the question is: how do animals remember? And approached at the cellular and molecular level, how do individual neurons come to represent elements in their environment (e.g., objects)?

Hebb (1949) was among the first to formalize a theoretical principle of how the activity, or more accurately the co-activity, between neurons could produce lasting changes in the structure of the nervous system by stating that "When one cell repeatedly assists in firing another, the axon of the first cell develops synaptic knobs (or enlarges them if they already exist) in contact with the soma of the second cell." This view suggested not only that populations of neurons were engaged in the representation of information, but also that the patterns of connections (i.e., patterns of synaptic weights) between neurons may be causally involved in the representations of objects in memory, and that *recollection* would be seen as the reactivation of these neurons and connections.

Nearly a decade later in 1957, Brenda Milner (Hebb's student), together with William Scoville, described the appearance of a striking mnemonic deficit of one of

Scoville's patients after bilateral resection of his hippocampi(Scoville and Milner, 1957). Following surgery, patient HM appeared generally unimpaired in regards to speech and temperament. Strikingly however, he was impaired (though not completely) to form any new memories of persons or places following his surgery and even exhibited significant retrograde amnesia for several months leading up to his surgery. It appeared that an anatomical locus for memory had been found.

Two decades after Milner and Scoville's clinical report on HM, the first experimental support for Hebb's postulate arrived via a recording preparation from the dentate gyrus of rabbits (*in vivo* anesthetized and *in vitro* slices). Electrical stimulation of the perforant path fiber tract to the dentate gyrus had previously been demonstrated to result in a robust extracellular response of the underlying neuronal population. In the early 1970s several now classic papers (Bliss and Gardner-Medwin, 1971, 1973; Bliss and Lømo, 1973), reported that when this pathway was stimulated with a high frequency electrical impulse, subsequent test pulses showed a marked and long lasting enhancement of the population response, suggesting that a physiological change—as predicted by Hebb's postulate—had occurred. Guided by this constellation of theoretical proposals and empirical data, the last half century has seen an explosion of research into the neurophysiological correlates of information encoding in the nervous system. As a result, several facets of the organization of activity in the nervous system have begun to emerge: from the activity of populations of neurons, through the role of field potential oscillations, and finally temporal correlations in activity between neurons. The

remainder of this introduction will briefly introduce these ideas in order to contextualize and motivate the experiments contained in this dissertation.

Fundamentally, information is encoded in the firing rate of neurons, activity which is ultimately received and transformed by other neurons. In this context, a fundamental question in neuroscience is how spiking activity of single neurons is organized to accurately represent information and how an organism uses this information to guide its behavior. The dominant view of neural encoding is that neurons systematically increase or decrease their firing rate in response to stimuli to which they are selective. These responses range from relatively direct transformations of sensory stimuli such as those of neurons in the auditory system where subsets of neurons selectively respond to tones of certain frequencies, to the more abstract, such as those of hippocampal pyramidal neurons selective to an animal's location in an environment. As indicated above, the question becomes: how, given the vast amount of information presented to an organism over its lifetime, does the nervous system avoid interference between multiple—possibly similar—neural representations. A luminary in the field, Horace Barlow (1961, 1972) proposed that perhaps the simplest solution to this problem is that the brain can efficiently do more with less.

At the level of neuronal responses to sensory stimuli (i.e., firing rates), Barlow (1972) stated that the "aim of information processing in higher sensory centers is to represent the input as completely as possible by activity in as few neurons as possible." This view of organization of the nervous system has received tremendous empirical

support, especially in regards to the organization of information in the visual system. Decades of work have demonstrated how retinal signals are transformed into elementary shapes (e.g., lines and edges) and are then gradually transformed into abstract and view-invariant representations of objects in the environment, using successively fewer neurons at each level of processing. A potentially limiting factor to this view, especially in higher level visual areas, is that similar stimuli may inadvertently activate the neuronal population associated with another stimulus and thereby lead to an inadvertent error in memory (Figure 1A). One mechanism that could reduce interference between representations is an experience-dependent sharpening of the neuronal population, whereby two populations of neurons become more distinct (Figure 1B; Sakai et al., 1994; Desimone, 1996). Thus, a more distinct representation allows the brain to identify the correct stimulus more rapidly (Desimone, 1996). This mechanism would also explain perceptual learning data, which show that subjects generally show faster reaction times as a function of experience. Theoretically, it has been suggested that such a tuning mechanism may be instantiated via the selective expression of long-term depression (LTD) in the relevant cortical area. Recent data suggest that interfering with molecular processes related to LTD result produce an impairment in the expression of recognition memory (Griffiths et al., 2008a; Massey et al., 2008). However, as will be seen in Chapter 2 and pursued experimentally in Chapter 4, empirical support for the existence of such tuning mechanisms, especially in the medial temporal lobe, is tenuous at best.

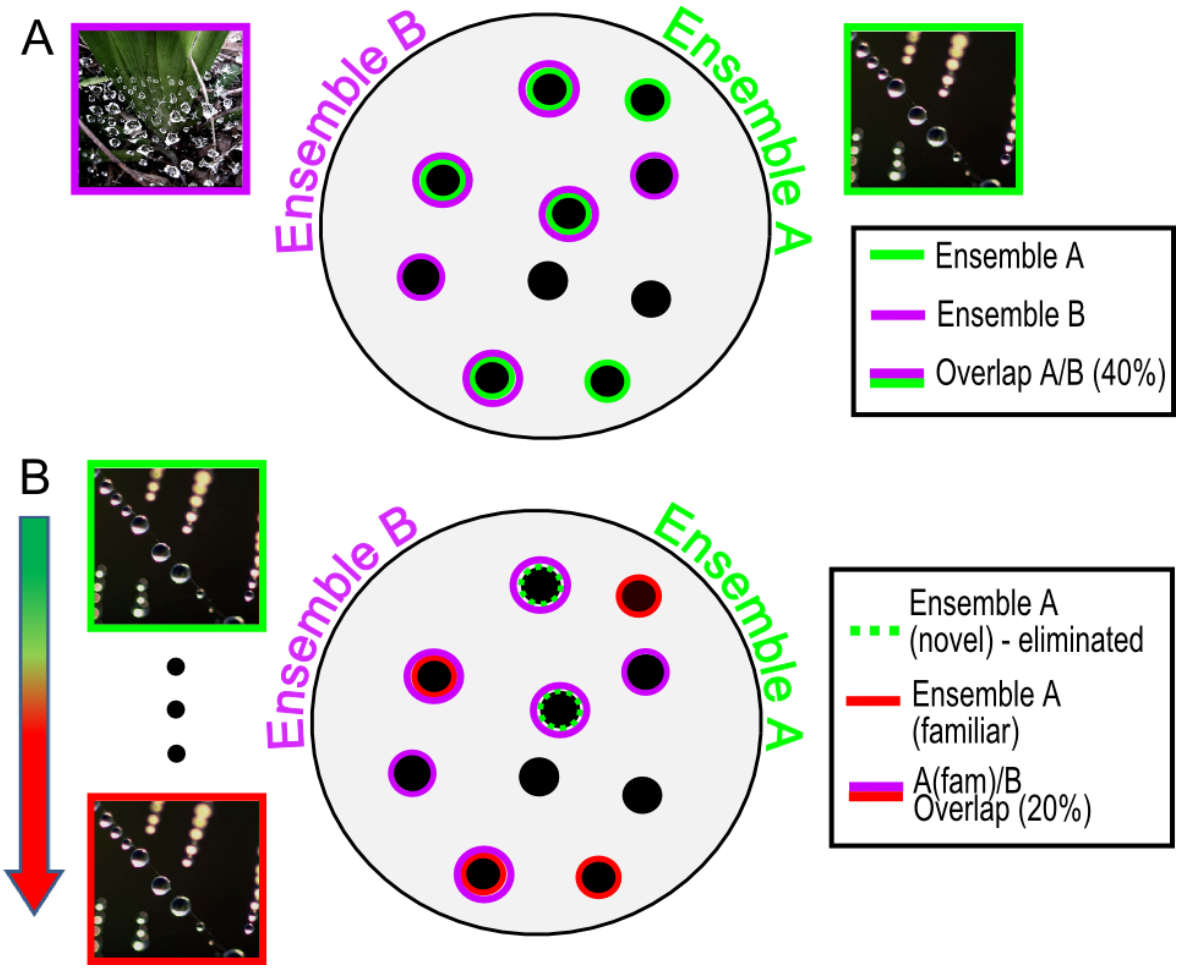


Figure 1.1 - Population Tuning
A. Theoretical distribution of activated population of neurons in response to two similar images. Black circles represent individual neurons, with the surround color identifying membership to different ensembles associated with an image. Note that given the high similarity between the two images that there exists a high degree of overlap between these images at the neural level (40% of the total population). This overlap may bias the network to inadvertently retrieve the image associated with ensemble A when presented with the image associated with ensemble B. **B**. Experience-dependent tuning of a neural representation. Populations of neurons may selectively increase the specificity of their representation by eliminating units with overlapping selectivity profiles from the population. The example in B outlines how, following multiple exposures, there may occur a reduction in the number of neurons selective to a particular image. In this case two neurons are removed from ensemble a (dashed green lines), reducing the population overlap (red/purple in B) by 50% to 20%, drastically lowering chances for inadvertent activation.

The transmission of information between two neurons proceeds via the propagation of electrical impulses via axons to synaptic contacts, and finally along elements of the receiving neurons' dendritic branch. This propagation of activity produces inward and outward fluctuations of current flow in activated synapses and dendritic branches which, when summed across a significant spatial scale, produces a characteristic and generally rhythmic electrophysiological signal known as the local field potential (LFP; Traub et al., 1989; Oren and Paulsen, 2010). Fluctuating field potentials were first described by Caton (1875) in animals and in humans several decades later by Hans Berger (1929), who hypothesized the observed potentials to be the physical instantiation of telepathic ability (Millett, 2001). While Berger's initial hypothesis has fallen out of favor, the role of these potentials in the organization of neural activity has become no less important.

Oscillations in the local field potential have been observed across a variety of species (from locusts to humans) and behaviors ranging from attention to motor execution are suggested to be signatures of interlaminar (von Stein et al., 2000) and interregional communication (Colgin et al., 2009a; Cohen et al., 2011). Of central interest to the question of neural encoding, however, is whether and how these oscillations are able to regulate the spiking activity of individual or population of neurons. In this context, two of the best neuro-behaviorally characterized oscillations are theta oscillations of the hippocampal formation, and gamma oscillations, which are seen throughout the cortex of mammals and also appear in some insects.

Theta oscillations (7-12 Hz) in the rodent hippocampus are arguably the best characterized types of oscillations in regards to its physiological origin and computational mechanism. Vanderwolf (1969) was among the first to describe the rhythm's strong correlation with motor behaviors such as running, exploration, and more recent studies in humans show similar correlations with spatial exploration (Ekstrom et al., 2005). Strikingly, place-selective CA1 pyramidal neurons burst at theta frequency. This correlation suggests a functional link between theta oscillations and the spiking activity of CA1 pyramidal neurons.. When examined more closely, the relative timing of spikes in relation to the ongoing theta oscillation is such that when an animal first enters the portion of the environment to which a neuron is responsive to, the cell fires spikes at a particular phase of theta (Figure 1 A). As the animal progresses through this location, the spikes of the neuron fire at successively earlier phases of the theta oscillation until the animal exits the location and the spikes have precessed one full theta cycle (Skaggs et al., 1996; Maurer et al., 2006; O'Keefe and Recce, 1993; Figure 2 Ab & Ac). Underscoring the importance of the theta rhythm, pharmacological disruption of theta oscillations (which do not disrupt the firing rate of neurons) significantly impairs navigation related abilities in rodents and humans (Robinson and Riedel, 2004; Robbe et al., 2006).

In contrast, gamma oscillations (40-100Hz) exhibit much smaller amplitude field potential than theta oscillations, whose activity generally reflects the activity of inhibitory synaptic currents (Hájos et al., 2004; Bartos et al., 2007; Tukker et al., 2007a).

These oscillations have been identified in a variety of brain regions and experimental preparations and their appearance is most generally related to behaviors that require attention. The primary role of gamma oscillations appears to be inducing synchrony among spikes such that spikes tend to fire at consistent phases (e.g., trough, Fig 2Ba) of the gamma oscillation (Milner, 1974; Gray and Singer, 1989; Von Der Malsburg, 1994). Behaviorally, it has been demonstrated that spike/gamma relationships in V4 are enhanced during visual attention and that functionally this relationship reflects a more precise timing of action potentials to a given stimulus (Fries et al., 2008). Similar results having been obtained from the olfactory bulb of locusts (Stopfer and Laurent, 1999). Additionally, *in vitro* recordings in hippocampal slices have demonstrated that CA1 pyramidal neurons tend to fire most regularly when stimulated with a sinusoidal current injection either at theta frequency or gamma frequency (Fellous et al., 2001). Finally, recordings from CA1 of rhesus macaques have shown the presence of enhanced coherence between gamma oscillations and spiking activity of single neurons during stimulus encoding while the animal performs a passive visual recognition task. Importantly, the magnitude (or strength) of the coherence between gamma and spikes are linked to subsequent recognition performance, with larger coherence values being linked to better performance. These data suggest that gamma oscillations may facilitate mnemonic encoding and cell assembly formation (Jutras et al., 2009 ; Figure 2 Bb).

Oscillations are involved both in organizing spiking activity of single neurons and possibly causally involved in synchronizing the activity between neurons and regions at

millisecond time scales. Implicit in this view is that an ensemble of neurons (a group of neurons participating in construction a neural representation of a scene or object) should exhibit temporal interactions, or even synchrony, and that higher order correlations between neurons may be the ultimate signature of neural encoding.

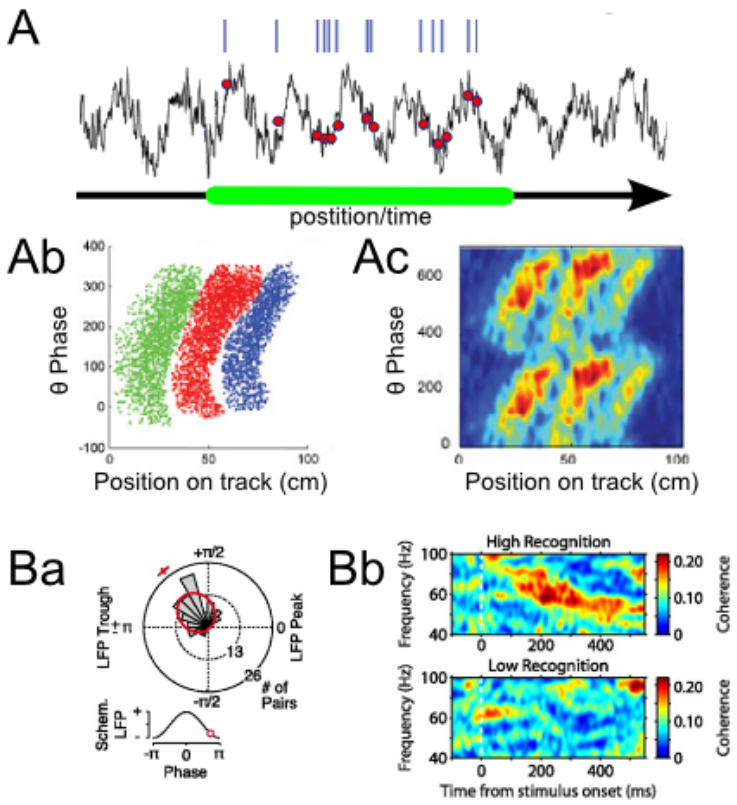


Figure 1.2 - Phase of Coding
A. Relationship of spikes for a CA1 pyramidal neuron relative to the hippocampal theta rhythm during place field traversal (place field size indicated in green). Note the precession of spikes (in red on the LFP trace, and blue above trace) relative to the ongoing theta oscillation. As the rat enters the place field, neurons fire preferentially at the peak of the theta, and fire at increasingly earlier phases until spiking returns to the peak. [From Scholarpedia - Hippocampus (G. Buzsaki,D. Robbe)]. **Ab.** Example of three pyramidal neurons expressing overlapping place fields. Spikes from each place field exhibit characteristic precession through theta phase as a function of position. Colors represent spikes from different cells (Maurer et al., 2006). **Ac.** As in Ab but converted to spike density map (Maurer et al., (2006). **Ba.** Example of spike gamma (~35Hz) phase relationships from primate prefrontal cortex. Ba(top) Simultaneously recorded spike-LFP pairs, LFP filtered at gamma frequency (~40 Hz). The radial position (0 to π) of the vector indicates the phase position (between peak and trough) while the magnitude of the radial

vector indicates the number of observations of spike/lfp pairs at a particular phase position. Note the consistent spike/phase relationship with the majority of spikes occurring near the trough of the oscillation, when inhibition is minimal (Ba - lower portion(Siegel et al., 2009). **Bb.** Spike gamma coherence in monkey hippocampus during encoding period of a visual recognition memory task (Jutras et al., 2009). Encoding trials were sorted by subsequent recognition performance. Note the significantly enhanced gamma band coherence during trials in which the animal recognized the stimulus trials. The findings are interpreted to suggest the formation of gamma coherent cell assemblies.

The notion of correlated activity in the nervous system as a feature of information encoding in many ways is a return to Hebb's "fire together, wire together" principle (Schatz, 1992). The study of correlated activity in the nervous system focuses across a range of temporal scales, from milliseconds to seconds, and spatial scales, from a cortical column to intra-regional connections. Generally speaking, however, of key importance is whether and how two temporal processes are statistically dependent on one another.

Historically, the most basic measure of spike timing correlations is the cross-correlogram (CCG). In its most basic form, the CCG counts the occurrence of the spikes of neuron A relative to that of neuron B. If the timing of spikes between two neurons is completely independent, the CCG will be effectively flat. However, if there exists a temporal dependence between the spikes of two neurons such that, for example, neuron B consistently fires at some temporal offset relative to that of neuron A, the CCG will show a shifted peak. Alternatively, if the two neurons are driven by a common input, they will show a strong central peak (e.g., Griffith and Horn, 1963; Perkel et al., 1967; Perkel, 1975; Toyama et al., 1981; Aertsen et al., 1989; Reyes et al., 1998; Swadlow, 2002; Thomson and Lamy, 2007). CCGs can serve as powerful indicators of

functional connectivity patterns between local or spatially segregated neurons. Recently, Takeuchi et al. (2011) were able to demonstrate that changes in the features of CCGs among neurons in different cortical layers were representative of changes in the direction of information flow between cortical layers of primate temporal cortex, thereby matching theoretical models of this region. While the precise anatomical connectivity between the sampled neurons is unknown, several *in vivo* and *in vitro* approaches have combined different cell labeling methods and have found connectivity patterns generally supportive of the idea that these temporal correlations may be linked to anatomical connections (Toyama et al., 1981; Palm et al., 1988; Aertsen et al., 1989; Thomson and Lamy, 2007).

Temporal correlations between neurons across a multitude of time scales are modified by a variety of factors including experience (Wilson and McNaughton, 1994; Hoffman and McNaughton, 2002), attention (Cohen et al., 2010), stimulus features (e.g., luminence) (Maldonado et al., 2000; Kohn and Smith, 2005), motor planning (Vaadia et al., 1995), as well as local levels of neuromodulators (Joshua et al., 2009). However, estimates of correlation strength may be confounded by experimental factors such as spatial sampling scale, the quality of single unit isolation, and electrode drift in acute preparations (Gutnisky and Dragoi, 2008; Ecker et al., 2010; Schulz and Carandini, 2010).

From a theoretical perspective, the benefits of using temporal correlations to encode information is that it provides an expedient means of dealing with the binding problem: that is, how does the brain functionally link together disparate neurons that

must coordinate their activity to construct a neural representation (e.g.,(e.g. Gray and Singer, 1989; Salinas and Sejnowski, 2001)? Temporal correlation coding is consistent with the notion of gamma oscillations binding together neurons into a stable representation (Engel et al., 2001a; Fries et al., 2007).

However, several empirical and theoretical challenges exist that question whether neural systems actually use a correlation code. Multiple unit recordings from V1 (Gutnisky and Dragoi, 2008; Ecker et al., 2010), supplementary motor cortex (Oram et al., 2001), prefrontal cortex (Averbeck et al., 2003) and the retina (Nirenberg et al., 2001) all demonstrate that correlations between neurons at a variety of time scales carry, at best, approximately 10% more information than that conveyed by the activity of single units (Shadlen and Newsome, 1998; Rolls et al., 2003). This suggests that, from an information capacity perspective, correlations add relatively little. Moreover, Shadlen and Newsome (1998) have argued, based on a combination of theoretical and electrophysiological data, that in cortical neurons operating under a high-input regime (e.g., densely connected high firing rate neurons) temporal correlations must emerge but "do not reflect anything special".

From an encoding perspective, it has been argued that correlated activity may make a representation more robust (e.g., Salinas and Sejnowsky 2001). However, other accounts have argued that **a)** the maintenance of correlations that are redundant is energetically inefficient and ultimately requires an elimination of those redundancies (Figure 3A;Laughlin et al., 1998) and that **b)** correlations may degrade network

performance by enhancing the possibility of activating the wrong population of neurons (Barlow, 1961; MacGregor and Gerstein, 1991; Gutnisky and Dragoi, 2008). Implied by these counterpoints is the notion that neural systems may be better served by having the activity between neurons be relatively uncorrelated.

Several recent studies from primary somatosensory and visual cortices of rodents, as well as from rhesus macaques, demonstrate that when large populations of well-isolated simultaneously recorded neurons are observed, the magnitude of correlations between these neurons is much smaller than previously estimated (Gutnisky and Dragoi, 2008; Ecker et al., 2010), suggesting that asynchrony may be a default state of the cortex. The authors of these studies highlight several experimental factors, which could have biased previous estimates of correlated activity within cortex, including activity fluctuations induced by anaesthesia and poor single unit isolation.

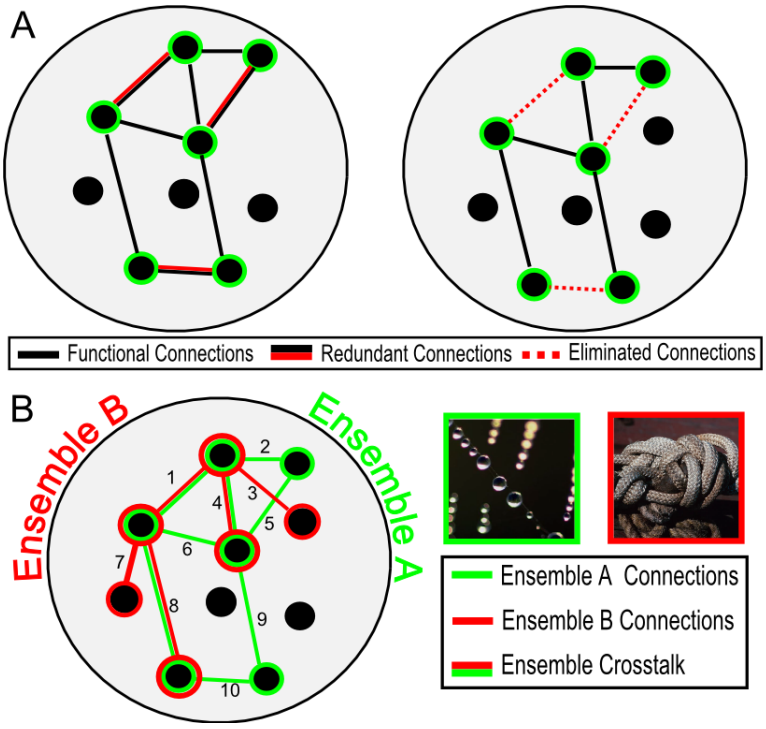


Figure 1.3 - Tuning of Functional Network Interactions
A. Eliminating redundancies. Redundancies in "functional" network architecture may be energetically inefficient. Eliminating the redundancies not only preserves energy but also produces a more distinct and efficient code. **A (left),** note redundant "functional" connections in the ensemble (red/black). Integrity of the ensemble is maintained when redundant correlations are eliminated (red-dashed), as all necessary elements are still bound together via mutual connections. **B. Ensemble Crosstalk.** Two ensembles (A and B) within a neuronal population representing two images (green and red respectively) and the "functional" connections between ensemble elements (numbers). In a temporal correlation schematic, ensemble topology is characterized by correlations (i.e., functional connections - colored lines) between its constitutive elements. Overlap in these correlations can result in crosstalk between ensembles. The structure of ensemble B (red) is characterized by connections (1,3,4,7,8), while A is embodied by (1,2,4,5,6,8,9,10). Activation of the connections in ensemble B may inadvertently lead to the activation of ensemble A, if there exists a mechanism (possibly Hebbian in nature) that has strengthened these connections sufficiently. In the present example, activation of ensemble B produces activity in elements 1,4, and 8, which are overlapping with the structure of A. If these connections have previously undergone Hebbian potentiation, there exists the possibility that the activity in these branches leads to the activity of 5,6,9,10. This inadvertent activation could lead to the inappropriate "recall" of the ensemble B. Eliminating overlap (not shown), by removing the connections 1 and 8 from ensemble A, preserves the overall topology of A while making the code more distinct and stable.

In summary, a wealth of data exists describing correlated activity in the nervous system across a variety of spatial and temporal scales. While correlations at very short time scales (1-3ms) appear to be robust markers of the connectivity between neurons, the role of correlations at longer time scales and whether these form a temporal population code appears more tenuous.

Critically then, there appear to exist two proposals regarding the organization of neural activity. Gamma oscillations are thought to synchronize neurons within and across regions, activity which has been shown to be associated with enhanced mnemonic recall. Conversely, recent theoretical and empirical data suggest that previous estimates of correlations between neurons may have been drastically overestimated and that their existence may even be detrimental to neural encoding. Furthermore, hidden within the Hebbian leitmotif of "Fire together, Wire together", is a fundamental flaw. Specifically, if neurons are continuously "wiring together" there must be a mechanism of depotentiating subsets of these connections in order to, avoid cross-talk between representations (Figure 3B).

The objective of the current dissertation is to investigate the nature of population coding within the medial temporal lobe of the behaving macaque and to develop an understanding of how different codes emerge as a function of experience. The questions addressed by this dissertation directly relate to how the brain dynamically balances the need to link neurons into functional information processing units (e.g.,

ensembles) while at the same time ensuring efficient encoding and reducing the risk of runaway synchrony.

Towards this end, this dissertation will draw upon data recorded from four primates performing a passive visual recognition task. In total, we recorded the activity of 633 neurons, many of which were simultaneously recorded. Data were taken across the medial temporal lobe, but generally came from the hippocampus (CA3/CA1), and the perirhinal cortex, with smaller portions of data coming from the entorhinal and parahippocampal cortex. The execution of these experiments in primates was warranted given differences in the structural organization of the medial temporal lobe between rodents and primates (see section 2.1.6) as well as the inherent similarity in the behaviors between nonhuman primates and humans.

Having reviewed some fundamental principles of information encoding in neural populations in this introduction, Chapter 2 will review the current state of knowledge regarding the role of medial temporal lobe structures in the process of recognition memory in primates. Specifically, the anatomical organization of the medial temporal lobe and how selective lesions to sub-regions within the medial temporal lobe lead to deficits in mnemonic performance—as well as recent controversy regarding their interpretation. The chapter will conclude with a discussion of the response properties of single neurons in these different regions and how their activity combines to form stable mnemonic representations. Having established a background within which to

contextualize the results, Chapter 3 will provide the reader with the general methods regarding animal training, surgeries, and data acquisition.

Chapter 4 focuses broadly on experience-dependent changes in the response properties of individual neurons and combines the results from individual neurons to examine changes at the population level. Specifically, the results will show that at the level of neural populations in the hippocampus and cortex, we do not find evidence for an experience-dependent retuning of the population response. In addition evidence for differential contributions of medial temporal lobe subregions to the mnemonic process is discussed.

Chapter 5 describes a series of analyses designed to test the predictions associated with the hypotheses that changes in novelty are reflected in the local field potential and that the brain may use this activity to modify spiking timing precision of individual temporal lobe neurons. Our analysis demonstrates a small but significant change in the amplitude of gamma oscillations as a function of experience. In addition, significant problems associated with methods of measuring spike-phase relationships is highlighted and the implications for the interpretations of findings in the literature is discussed.

The advantage of tetrode recording preparation to enable the acquisition of large numbers of simultaneously recorded neurons is discussed in Chapter 6. These data are used to address the hypothesis that one mechanism by which the brain produces efficient codes is to reduce the number of correlations within the population. The

results from this analysis indicate that cortical regions undergo an experience-dependent decorrelation, in line with recent theoretical and physiological results. Moreover, evidence is presented that this decorrelation could be a result of hippocampal processing. Finally we present evidence that gamma oscillations may play a functional role in driving these correlations when items are novel, in line with previous data, suggesting that gamma oscillations play a critical role for encoding and linking neurons into ensembles.

CHAPTER 2- BACKGROUND

2.1 Overview of MTL Organization

The medial temporal lobe (**MTL**) of the mammalian brain is a series of hierarchically organized structures that are recurrently connected. At the gross structural level, the medial temporal lobe is defined by four distinct subdivisions, spanning from the perirhinal (**PRC**) and parahippocampal (**PH**) regions and the entorhinal cortex to the hippocampus proper. The hippocampal formation is further subdivided into the dentate gyrus (**DG**), two CA regions (**CA1/CA3**)[1], and the subicular complex (**SUB**). The majority of inputs to these regions are cortical in origin, though not exclusively so. Within the medial temporal lobe, PRC and PH constitute the major input to the entorhinal cortex which in turn projects to the hippocampus proper. Hippocampal outputs return to their cortical origins via the subiculum and entorhinal cortex. This system of connectivity reflects the convergence of lower level sensory input into higher order association systems, and belies the structure's broader role in episodic memory and higher level perceptual processes (Murray and Bussey, 1999; Lavenex and Amaral, 2000; Brown and Aggleton, 2001a; Squire et al., 2004).

This chapter contains three interrelated sections which respectively review the anatomy, behavioral deficits that result from lesions, and the neural responses found in

[1] Notably, anatomical text often refer to the existence of a CA2 and a CA4 region. The CA2 function of this region is only poorly understood, but recent developments in functional imaging techniques are offering new avenues for dissecting its function. CA4, while seemingly separate retains the defining feature of the dentate gyrus in that it gives rise to fibers contained in the Schaffer collaterals

different regions within the primate medial temporal lobe. The discussion within each section progresses from cortical structures to hippocampal structures.

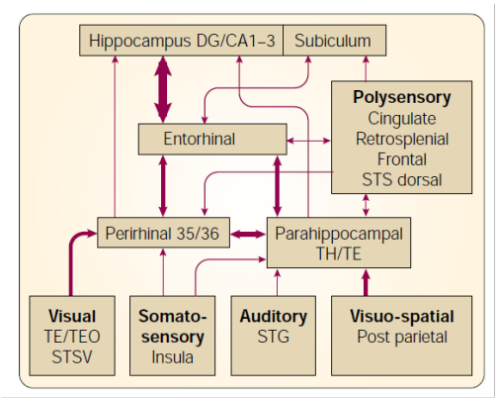


Figure 2.1 - Hierrachical and reciprocal organization of the medial temporal lobe
Gross anatomical organization of the medial temporal lobe. Arrows indicate direction of interactions and the thickness of the lines represents the relative strength of the connections between regions. Anatomical data indicate that the hierarchy can divided into 5 unique levels: early sensory, Perirhinal and Parahippocampal, Entorhinal, and Hippocampal, as well as polysensory. Importantly, while this image may suggest simple relay functions for perirhinal, parahippocampal and entorhinal regions, physiological and lesion data indicate that these regions each have unique computational contributions. Abbreviations: DG, dentate gyrus; EC, entorhinal cortex; POR, postrhinal cortex; STG, superior temporal gyrus; STS, superior temporal sulcus (v-ventral); TH/TF,TE/TEO, temporal area H,F,E/EO respectively; SUBIC, subicular complex. Modified from Brown and Aggleton (2001).

2.1.2 Perirhinal Cortex

In the rhesus macaque, perirhinal cortex **(PRC)** encompasses Broadman areas 35 & 36 and can be divided into 5 subregions based on distinct projection profiles and cytoarchitectonic characteristics (Suzuki and Amaral, 2003a). The roughly C shaped structure is situated laterally along rhinal sulcus and extends along the surface of the temporal lobe with its rostral limit at the fronto-temporal junction, terminating 2-3 mm beyond the rhinal sulcus (Insausti et al., 1987a; Burwell, 2000). Medially, the structure is

bounded by the entorhinal cortex. However, debate exists as to the exact anatomical boundaries (Saleem et al., 2007).

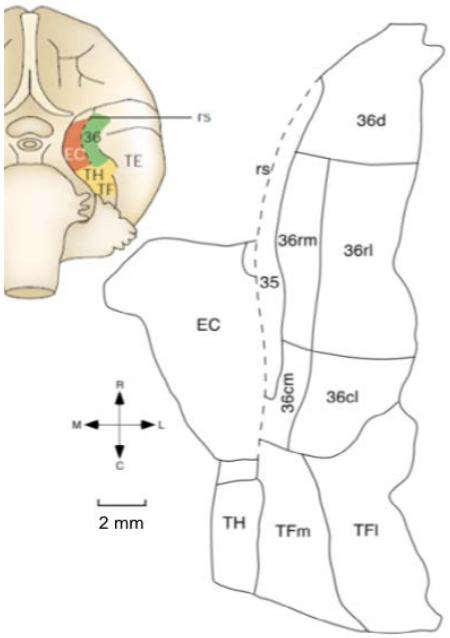


Figure 2.2 - Perirhinal Cortex
A. Ventral view of the macaque brain. Showing the gross anatomical relationships between different medial temporal regions (Not shown is area 35, see B). **B.** Unfolded map of entorhinal, perirhinal and parahippocampal cortex, including their respective subregions. Dashed line represents the fundus of the rhinal sulcus. Abbreviations: EC, entorhinal cortex; rs, rhinal sulcus; TH/TF,TE/TEO, temporal area H,F,E/EO respectively; 35, 36, perirhinal cortex (d - dorsal, rl - rostrolateral, rm - rostromedial, cl-caudolateral,cm-caudomedial). Adapted from: (A) Suzuki and Amaral (1994) and (B) Brown and Aggleton (2001).

2.1.2.1 Connectivity with Visual Cortical Regions

In the rhesus macaque, the majority of cortical projections to PRC arise from unimodal visual areas (TE/TEO, approximately 62%) and adjacent polymodal association cortices (TF/TH, approximately 25%; Suzuki and Amaral, 1994). As a consequence, projections to the PRC are largely devoid of inputs from visuospatial regions (e.g., parietal cortex), that

project preferentially to nearby TF/TH and whose termination patterns follow a much stricter topographic projection pattern (Lavenex et al., 2004). Smaller afferent projections arise from multiple insular subregions, as well as orbital frontal cortex (OFC), with the insular projection likely providing somatosensory and visceral information while the OFC likely provides reward/valence related information (Suzuki and Amaral, 1994c). Cortical afferents are largely distributed between layers III and V with minor innervations of superficial layers (Saleem and Tanaka, 1996). This pattern of projections reflects the feedforward organization of the flow of information to this region—from primary sensory to higher level visual association areas (Rockland and Pandya, 1979; Maunsell and van Essen, 1983; Felleman and Van Essen, 1991; Rockland, 1997).

Afferents from the Temporal Area E (**TE**) onto PRC targets show differential termination patterns depending on their origin. Anterior ventral (TEav) afferents project divergently to virtually all subregions (except 36d) of the PRC, while dorsal (TEad) afferents project in a highly convergent manner onto a very narrow region of 36r/c, covering less than 1/10th of the area of PRC (Saleem and Tanaka, 1996). The functional anatomical consequences of learning have been examined via parallel recordings from TE and PRC combined with multiple retrograde tracer injections. Localized injections of a retrograde tracer into area 36 mirrored previous findings of divergent projections from TE to PRC. However, injection of a different retrograde tracer into a region of PRC whose neurons showed enhanced responses to learned visual images revealed a significantly less divergent projection originating from visually responsive TE neurons,

while there was no difference in the nature of the projection from non-responsive TE neurons (Yoshida et al., 2003). The enhanced convergence onto neurons sensitive to learned visual images has been suggested to emerge from the acquisition of visual long-term memory, possibly resulting from axonal retraction. However, no additional studies exist confirming the result. Area 36d is unique in the organization of its afferents as these include only minor unimodal visual projections. This structure receives dense projections from neurons the superior temporal gyrus and sulcus (primarily TF/TH) (Suzuki and Amaral, 1994c). 36d projects heavily within itself and to area 35, suggesting that this area may serve to integrate poly and unimodal information streams (Lavenex et al., 2004).

All subregions of the PRC (except 36d) share extensive associational connections between each other and the adjacent areas TH/TF. The strongest of these intrinsic projections is between 36c and the anterior portion of TF (with posterior portions receiving relatively weaker projections), suggesting 36c as a major hub for connectivity between the two regions (Lavenex et al., 2004). The pattern of connectivity is such that projections from TF appear to be primarily feedforward in nature, while the return collaterals from PRC are primarily of feedback type, with the strength of the efferents being mirrored in the strength of the afferents (Lavenex et al., 2002, 2004).

PRC provides a set of widespread back projections to the cortex. These projections however are asymmetric, meaning that they do not fully reciprocate connections to all regions the PRC receives inputs from. Back projections target both

unimodal visual association areas (TE/TEO and V4) and multimodal superior temporal gyrus/sulcus (Lavenex et al., 2002), although the pattern of distributions of labeled neurons in these regions is not uniform. For example, anterograde tracer injections labeling projections from PRC to TE/TEO show very broadly distributed staining of cell bodies throughout both regions; suggesting that these return projections play a broader modulatory role. In contrast PRC back projections to frontal cortex are significantly more specific, targeting mainly lateral and medial orbitofrontal cortex. The more spatially restricted distribution of labeled neurons in these frontal regions is also much narrower possibly serving as a mechanism to integrate visual with reward and affective information in working memory (Lavenex et al., 2002). Cytoarchitecturally, the majority of the cortical return projections from PRC target all layers of the cortex except layer IV. This distribution of projections is consistent with feedback type projections, consistent with observations throughout the visual system (Pandya and Kuypers, 1969; Rockland, 1997).

Projections from PRC/PH to the Entorhinal Cortex (**EC**) follow a rostral-caudal topography such that caudal EC receives primarily PH inputs while rostral EC gets primarily perirhinal input (Figure 2.3, top right panel). Projections from PRC to EC originate primarily in Layer III and V and target deep and superficial layers of the EC (with the exception of the olfactory region; Mohedano-Moriano et al., 2007). Return projections from EC to PRC emerge primarily from Layer V neurons primarily targeting cells in layers II/III (Suzuki and Amaral, 1994a). These patterns of projections suggest

that PRC afferents to EC are mainly of feed-forward type, while projections from EC back to PRC are primarily feed-back in nature.

2.1.3 Entorhinal Cortex

The Entorhinal Cortex (**EC**) of the rhesus macaque is situated along the ventromedial portion of the temporal lobe and is generally regarded as the major interface between cortical structures and the hippocampus. A key cytoarchitectonic feature of EC is the conspicuous absence of an inner granule cell layer (Layer IV), which is replaced by a series of myelinated fibers known as the lamina dessicans. The region is divided into seven sub-fields according to their rostral-caudal location. There is some inhomogeneity along this extent, with neurons at the rostral level having a patchy appearance with large surrounding fiber bundles. More caudally, the cytoarchitectural features become distinctly more laminar and columnar (i.e., cortical) in appearance (Amaral et al., 1987).

At the gross anatomical level, cortical inputs to the rhesus EC are organized into three segregated bands, though some overlap occurs between them. Caudal EC (i.e.: E_{LC},E_{CL},E_{C}) receives strong inputs from parahippocampal regions (TF/TH) and STS (polymodal) and somewhat weaker inputs from the posterior cingulate and temporal pole. Rostral EC receives the densest and highly diversified cortical inputs, the strongest of which originate from the STS, orbitofrontal, and perirhinal cortex; relatively weaker projections arise from anterior cingulate, anterior insular cortex, and TE. Finally the

olfactory region (far rostral) of the EC is targeted principally by strong inputs from agranular insular cortex, PRC, OFC, periamygdaloid and other olfactory related structures (Insausti et al., 1987a; Mohedano-Moriano et al., 2005). Interestingly, the intrinsic connectivity of EC is such that there are relatively few intra EC connections between caudal, rostral and olfactory subregions suggesting that these intrinsic connections are involved in maintaining a functional segregation between inputs (Chrobak and Amaral, 2007). In the rodent, the functional consequence of the differences in inputs to different regions of the EC is reflected in the activity of single units, with medial-EC neurons showing significant spatial selectivity while lateral-EC neurons are more sensitive to non-spatial contextual information (e.g., Hargreaves et al., 2005; Hafting et al., 2005). While similar functional differences likely exist in the primate EC, no studies have been conducted to examine the anatomical distribution of response profiles of EC neurons.

EC Layer II neurons give rise to a strong projection (the perforant path) to granule cells located in the molecular layer of the DG and pyramidal cells in CA3. Layer III neurons project preferentially to CA1 and subicular neurons. Deep Layers (i.e. V/VI) receive return projections from CA1 and subiculum (Amaral et al., 1987; Saunders et al., 2005; Mohedano-Moriano et al., 2007). Neurons in layers V/VI project back onto layer II neurons, providing the only feedback type connectivity of the return circuitry of the hippocampus, as subicular and CA projections terminate preferentially in deep EC layers.

Cortical return projections from the EC are reciprocal, in that they target those regions from which the EC receives input In the case of the PRC, EC neurons in layer V send significant return projections to neurons in layer I PRC with the pattern of reciprocity varying along the rostral-caudal axis such that medial PRC regions have stronger reciprocity than do lateral regions.

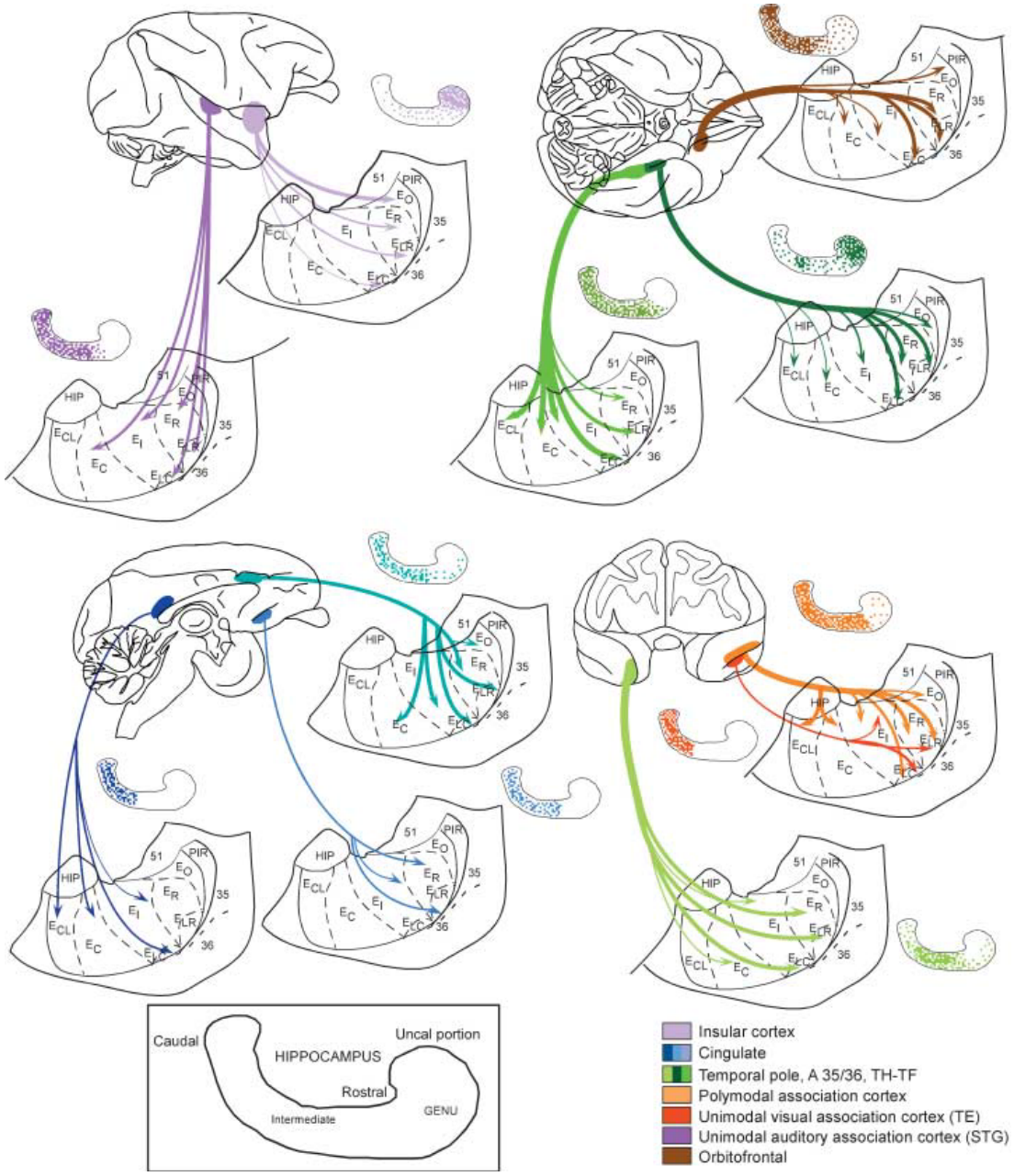


Figure 2.3 - Cortical projections to Entorhinal cortex

Meta analysis of cortical projections to EC subfields and EC efferent's to the hippocampus. Regional projections are color coded and the strength of the projection is represented by the thickness of the lines. Notably projections from insular cortex, temporal pole and PRC show a distinctly more rostral pattern of termination in the hippocampus, while TF/TH project more caudally indicating that the uncal portion of the hippocampus processes qualitatively different types of information than that of the remaining hippocampus. To date no studies have systematically examined differences in the activity of neurons along the rostral/caudal gradient. From Mohedano-Moriano et al., (2007).

2.1.4 Hippocampus

The hippocampal formation is the continuation of medial temporal lobe cortical structures, deriving its name from the similarity to seahorses of the structure's characteristic S shape. Due to the increased cortical size in primates, the hippocampus is forced inward during ontogeny such that it lies nearly horizontally within the medial temporal lobe. The hippocampal formation is composed of the dentate gyrus (**DG**), the CA fields (**CA1-CA3**) and the subiculum, connected via a series of (largely) unidirectional pathways known as the trisynaptic circuit. Historically, the flow of information has been described as follows: EC ➔ DG (synapse 1) ➔ CA3 (synapse 2) ➔ CA1 (synapse 3). However, more recent work (see figure 2.4) has demonstrated that there is significantly more interconnectivity and that the unidirectionality of trisynaptic pathway must be revised. The variety of cortical inputs and their subsequent mixing within the hippocampus underscore the fundamentally associative nature of processing within this structure and suggests its broader role in the construction of episodic memory.

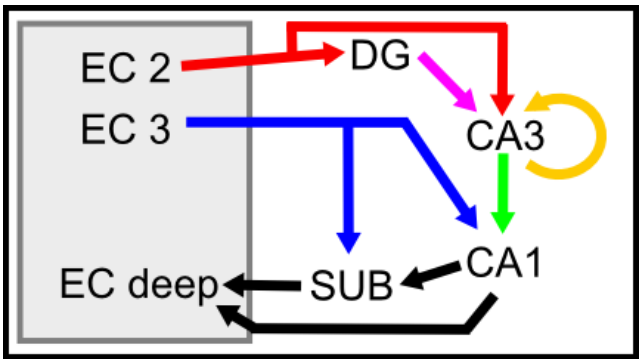


Figure 2.4 - Flow of information through the hippocampus
Updated diagram of the flow of information through the hippocampus starting at Entorhinal cortex (EC). EC Layer II cells send projections via perforant path to dentate gyrus (DG) and CA3 (RED). EC III neurons project directly to CA1 and the subiculum via temporoammonic pathway (BLUE). DG mossy fibers innervate CA3 (MAGENTA). CA3 sends an auto-associative projection to itself (YELLOW) as well as a projection to CA1 via Schaffer collaterals (GREEN). CA1 sends both direct and indirect (via Subiculum (SUB) projections directly back to the deep layers of the EC.

2.1.4.1 Dentate Gyrus

The primary projection to the dentate gyrus (**DG)** is via the perforant path fibers originating Layer II EC. As in the rodent, these efferents target synapses on the outer dendritic segments of DG granule cells (**GCs**) (Witter et al., 1989). The dentate gyrus of rhesus macaques contains approximately $1 * 10^7$ granule cells, an order of magnitude greater than in the rodent (Amaral and Lavenex, 2006). Layer II of the macaque entorhinal neurons contains approximately 165,000 neurons (Gazzaley et al., 1997; Merrill et al., 2000) and its efferent fibers terminate widely within the granule cell layer, with each fiber contacting up to 15,000 granule cells (Tamamaki and Nojyo, 1993). The large terminal arborizations of EC neurons onto DG GC dendrites along with a 60:1 ratio of granule cells to EC Layer II projection neurons indicates that a massive divergence of information occurs between the two structures. The functional implications of the observed divergence will be further discussed below.

Granule cell axons are called Mossy fibers (**MF**), that extend through the dentate hilar region to transverse the full extent of the CA3 field at approximately the same rostral/caudal level as the origin of the projection, similar to what is seen in rodents (Kondo et al., 2008). MFs form connections with the proximal dendrites of Mossy cells located in the dentate polymorphic layer. MF projections to CA3 target the proximal dendrites of pyramidal neurons via large asymmetric synapses. In rodents, the average MF contacts approximately 11-15 pyramidal cells and 7-10 mossy cells, although on average the convergence onto common pyramidal cells by neighboring granule cells is extremely low (Acsády et al., 1998). MF synapses onto CA3 pyramidal neurons can be extremely powerful with up to 40 active sites contacting a single post synaptic neuron. The total number of pyramidal cells in CA3 and the probability of connection by a granule cell suggest that each pyramidal cell receives input from approximately 72 GCs, based on data from rodents. MF synapses in both rodents and monkeys, are primarily glutamatergic, although immunohistochemical staining shows clear co-localization with GABA as well as terminals containing a number of neuropepetides (Sandler and Smith, 1991; Kondo et al., 2008). The functional consequence of the GABA/Glutamate co-localization is unclear.

In addition to the projection to Mossy cells and CA3 pyramidal neurons, MFs give rise to a second set of smaller collaterals which synapse onto interneurons within the hilar region of the dentate gyrus as well hippocampal CA3 stratum lucidum (Amaral, 1979; Gulyás et al., 1992; Seress et al., 2001; Kondo et al., 2008). In both the hilar

region and CA3 the contacts with interneurons are via small filipodial extensions which form a large number of small asymmetric synapses near cell bodies and spines (Acsády et al., 1998). Consequently, in addition to forming a major excitatory drive to CA3 there exists a parallel inhibitory drive that likely regulates overall CA3 excitability.

Functionally, it has been suggested that the highly divergent projection pattern of DG GCs to both excitatory pyramidal cells and inhibitory interneurons in CA3 may effectively reduce densely encoded cortical codes to more sparse codes thereby maximizing information encoding (Treves and Rolls, 1992; Acsády and Káli, 2007). A fuller discussion of this hypothesis requires and more detailed discussion of the physiology of DG GCs and which will be further examined in section 2.3.5.

2.1.4.2 - CA Fields

The CA fields, broadly divided into four subfields (CA1-4) are composed of a single pyramidal cell layer approximately 10-15 cells wide. In the rhesus macaque, CA1 and CA3 each contain approximately 1.3 million pyramidal neurons (Amaral and Lavenex, 2006). Pyramidal neurons possess an apical dendritic tree extending into the stratum radiatum towards the hippocampal fissure, as well as a basal dendritic tree which projects through the stratum oriens. In CA3 there is considerable variability in the size of the cells bodies (300-700 μm^2) and lengths of their projections (8-10mm vs. 16-18mm in rodents; Ishizuka et al., 1995). In contrast, the dendritic arborization of CA1 pyramidal neurons is significantly more homogenous (~13 mm in the rat), showing

similar architecture throughout. In addition to the large number of pyramidal neurons, there exist highly heterogeneous population of interneurons interspersed within the different layers of CA1/CA3 which shape flow of information through the hippocampal network (For further review (in rats) see: Freund and Buzsáki, 1996). As discussed previously, the MF of the dentate gyrus granule cells provide a major projection to CA3 region. CA3 pyramidal neurons give rise to two types of afferents, associational fibers which project back on itself, as well as the Schaffer Collaterals which form the major input to CA1. Notably, in rodents there exists a third projection via the hippocampal commissure. This projection is absent in primates (see section 2.1.6 for discussion of the differences between the rodent and primate).

The CA3/CA3 auto-associational projections arise from CA3 pyramidal neurons which form asymmetric excitatory synapses on both principal cells and interneurons (Witter, 2007). These synapses constitute a significant input to CA3 (see figure 2.4). In the rat, CA3 pyramidal neurons most proximal to the dentate gyrus contribute relatively few fibers to the associational projections projecting primarily to other distally located cells. In contrast, neurons at distal levels (i.e., further from the dentate gyrus) project along significant portions of the entire transverse axis of CA3, with some variation in the termination pattern across the dorsal/ventral extent (Ishizuka et al., 1990; Amaral and Lavenex, 2006). However, it has also been suggested that the associational projections are organized along longitudinal patches extending several hundred microns in anterior

and posterior directions, while retaining a narrow transverse pattern around the level of the cell body (Li et al., 1994).

The recurrent architecture of the CA3/CA3 projections has been compared in form to the structure of autoassociative neural networks. This perspective on information processing has been highly influential in attempts to understand the function and nature of information processing of CA3 (Treves and Rolls, 1994; McClelland et al., 1995). During learning, autoassociative networks have matched input and output patterns. Consequently, activated units undergo enhancement according to a basic (e.g., Hebbian) learning rule, ensuring that a stable representation of the entire episode is encoded within the network. Once a pattern is encoded within the network, subsequent presentations of partial or corrupted patterns to the network will correctly recall the previous instance of the full pattern (McNaughton and Morris, 1987a).

The axons of the CA3 pyramidal cells form one of two major projections to the CA1 region. Schaffer collaterals travel along the entire transverse extent of CA1 and extend significantly in both rostral and caudal directions. In the monkey, the rostral/caudal extent of these projections is close to 14mm, more than 3/4ths of the full rostral caudal length—suggesting the potential for a massive degree of integration occurring in the hippocampus. Proximally located CA3 neurons preferentially project to the stratum radiatum while distally located neurons preferentially innervate the pyramidal cell layer and stratum oriens (Kondo et al., 2009). In the rodent, the proximal/distal location of a CA3 neuron biases the extent of projections within CA1

(Figure 2.5 A); while in the macaque, projections tend to be significantly more uniform along the entire transverse axis. Interestingly, projections arising in the uncal region tend to remain restricted to rostral regions (Kondo et al., 2009), an observation in line with projection patterns from EC (Mohedano-Moriano et al., 2007). This suggests a possible segregation of information processing stream through the hippocampus—though the horizontal connectivity between these two "paths" has not been fully explored.

Input from the entorhinal cortex via the perforant path forms the second major input to the CA fields. Similar to the rodent, the rostral-caudal origin of layer III fibers to CA1 determines the transverse extent of termination (Figure 2.5B). These projections originate from a narrow band of neurons in the medial-lateral axis and project along the entire rostral/caudal extent of the entorhinal cortex. In contrast to the rat (in which afferent projections are highly laminated), EC projections to CA1 in the monkey preferentially terminate across the full extent of the stratum lacunosum-moleculare of the CA fields (Witter and Amaral, 1991).

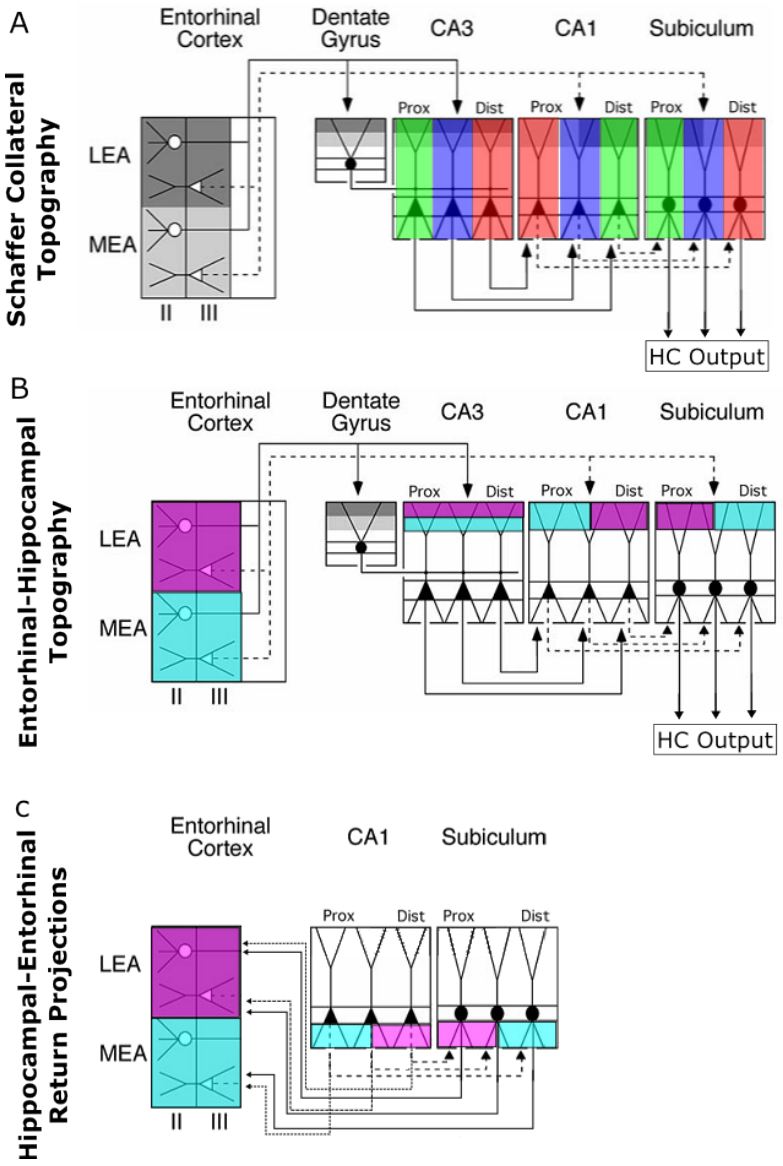


Figure 2.5 - Topography of transverse hippocampal projections (in the rodent)
Designation of principal cell location as proximal/distal refers to a cells location relative to the dentate gyrus. **(A) Schaffer Collaterals.** Proximally located principle cells in CA3 (green) project to distally located CA1 neurons, which in turn project to proximal cells in the subiculum. Note the reverse pattern of projections distal CA3 principal cells (red). **(B) Perforant Path.** Layer II neurons of MEA/LEA (Medial/Lateral Entorhinal Cortex), project to dentate gyrus and CA3, while Layer III neurons project to CA1 and the subiculum. Note the parcelation of MEA/LEA projections within the different hippocampal subregions (purple - LEA, turquoise - MEA) . **(C) Return Projections** CA1 and Subicular neurons reciprocate the projections to entorhinal cortex. The segregation of projections within the hippocampal formation raises the possibility of distinct processing "channels" through the Hippocampal formation, though there clearly exist several regions of overlap in afferents such as in CA3. Figure modified from (Amaral and Lavenex, 2006).

In addition to inputs arising from cortical origins, the hippocampus receives a large variety of subcortical inputs (for an extensive discussion see Amaral and Cowan, 1980). The origin of these projections may be broadly divided into amygdalar, thalamic, and brainstem. Projections from the amygdala to the hippocampus appear to arise from throughout the amygdala with some variation in the density of the inputs. Accessory basal and basal nuclei of the amygdala provide the most significant projections to rostral portions of the CA fields and the prosubiculum, terminating throughout the entire extent of the stratum moleculare, and stopping abruptly at the CA1/Subicular border (Aggleton, 1986).

Thalamic nuclei project widely to the macaque hippocampal formation (see: Amaral and Cowan, 1980); of these, two have received particular attention, the lateral nucleus as well as the reticular nucleus of the thalamus. In both the rodent and macaque, there is a significant projection from the lateral dorsal nucleus of the thalamus to subicular and entorhinal areas, thought to contribute head direction information crucial for navigation related activity (e.g. Mizumori and Williams, 1993).

The hippocampus also receives a number of neuromodulatory inputs. The major cholinergic inputs arise via projections from the medial septal nucleus via the fimbria terminating throughout the stratum oriens and stratum radiatum of the CA fields, with a relatively minor projection to the molecular layer of the dentate (Amaral and Cowan, 1980). Lesions of the medial septal nuclei produce overt deficits in spatial behavior and reduced theta rhythm modulation (Winson, 1978; Leutgeb and Mizumori, 1999).

Additional neuromodulatory projections arise from a variety of sources, with noradrenergic and dopaminergic afferents arising from the locus coeruleus and ventral tegmental area respectively (Oleskevich et al., 1989; Gasbarri et al., 1994).

2.1.4.3 - Hippocampal Return Projections

CA1 gives rise to two major efferent systems projecting primarily to the subicular complex and secondarily to the deep layer of the entorhinal cortex. CA1 fibers project throughout the pyramidal and molecular layer of the subiculum in a topographic fashion; distally located CA1 neurons project to the proximal subiculum including the CA1/Subicular border zone while proximal CA1 neurons project to distal subicular targets. Subicular projections continue through to the pre and parasubiculum and also provide a strong connection to deep layers of entorhinal cortex (Figure 2.5; Amaral and Lavenex, 2006).

In rodents, the return projections from subiculum to the entorhinal cortex are as follows: temporal (ventral) levels of the subiculum project to medial entorhinal cortex while septal (dorsal) regions project to lateral entorhinal areas (Amaral and Lavenex, 2006). In addition, the subiculum projects to the nucleus accumbens, medial mammilary nucleus, retrosplenial cortex, cingulate and olfactory nuclei, and various prefrontal regions. Importantly, in cases where the targeted region provides a strong projection to the subiculum, the subicular projection is fully reciprocal, a pattern believed to be preserved in the primate. In primates, there are only relatively meager commissural

projections from the CA fields to the contralateral hemisphere, there exists a major topographically organized subicular-entorhinal commissural projection which originates from the entire rostral-caudal extent (Amaral et al., 1984; see section 2.1.6 for further discussion of commissural connections). The observed point-to-point reciprocity of connections between these regions characterizes a highly preserved pattern of input-output mappings within the entorhinal cortex and closing the entorhinal-hippocampal loop (Amaral and Lavenex, 2006).

Entorhinal efferents project throughout the temporal lobe, including area TH/TF, PRC, Superior temporal gyrus (TA & TE), as well as amygdalar nuclei and several olfactory areas (Kosel et al., 1982). It should be noted that, in contrast to the rodent entorhinal-cortical, reciprocity is much more extensive and widespread (see section 2.1.6).

In addition to routes to the cortex through the subiculum and entorhinal cortex, there exists a direct cortical projection from area CA1 to several polysensory association areas. These projections are organized as longitudinal strips along large parts of the rostral-caudal axis of the hippocampus while only occupying a fairly narrow space of the transverse axis. Regions targeted by these projections extend into several uni- and poly-sensory as well as polymodal association areas including[2] (but not limited to): TE, TF/TL, PRC, TFO (Iwai and Yukie, 1988; Blatt and Rosene, 1998). However, the function of this

[2] An excellent summary of the banded projection patterns can be found on page 110 of Blatt and Rosene (1998).

projection and whether the two projections carry different kinds of information remains unclear.

2.1.5 - Conclusions: Integrative hierarchy of information processing

The medial temporal lobe is a hierarchically organized and reciprocally connected system whose structure suggests two primary functions: *association* and *consolidation*. The variety of cortical efferents projecting through the perirhinal cortices via the entorhinal cortex and into the hippocampus proper indicates that these structures are able to rapidly integrate and associate a vast and highly heterogeneous array of inputs, thereby enabling the integration of spatial-temporal contexts with different sensory inputs.

In addition to the feedforward hierarchy of associativity there exist widespread back projections from the hippocampus to the neocortex. Theoretical proposals have suggested the functional role of back projections to the neocortex is the consolidation of memories in the cortex: that is, by rapidly associating two disparate cortical inputs within the hippocampal circuit, cortical back projections are able, over time, to build a cortically based representation, independent of the activity of the hippocampus (Marr, 1971; McClelland et al., 1995). This theory is supported by observations that lesions of the hippocampus result in anterograde amnesia and amnesia for relatively recent events, while remote events are spared (e.g., Kim and Fanselow, 1992). It should be noted however, that lesions in humans and animals do not always produce consistent behavioral impairments. Notably, several experiments have demonstrated that

retrograde amnesia can, in some cases, be virtually absent – in obvious contradiction to the standard model of memory consolidation. In addition there often exist significant sparing of information which was learned during the period of retrograde amnesia (for review see: Nadel and Moscovitch, 1997). These inconsistencies, among others, led to a revision of the standard model and ultimately to the formulation of the multiple trace theory (**MTT**) of memory consolidation (Nadel and Moscovitch, 1997).

Similar to the standard model, MTT proposes that the hippocampus acts to rapidly encode new information from a variety of cortical sources. Encoding (or storage) of an episode results in the generation of an index which represents the cortical location of the elements of an episode—the creation of a trace (Teyler and DiScenna, 1986). Where the two models diverge is the prediction by the MTT that any time the hippocampus encodes a new episode additional traces are created. Re-activation of a previous trace results in the instantiation of a related, though not necessarily overlapping trace. As multiple traces accumulate, they can be utilized to extract factual information. In addition, the "strength" of a memory is not defined by the strength of the synapses representing a particular episode, but rather is related to the number of traces supporting it. MTT suggests that relatively recent memories (or traces) are particularly vulnerable as there exist only relatively few traces supporting them. Importantly, in this view, the hippocampus is always involved in the recollection of a memory, in contrast to previous models of hippocampal/neo-cortical interactions.

Finally, feedback projections to the neocortex from the CA1 region can be delineated along direct and indirect (subicular/entorhinal) and direct projections from CA1, implying significant redundancy in hippocampal output. While the backprojections themselves likely serve to consolidate neocortical information, the redundancy of these projections may instantiate a sophisticated mechanism of *fidelity control,* such that only those neurons (or group of neurons) activated by both direct and indirect projects will be tagged for consolidation. Such a mechanism could serve a powerful error correcting function, by effectively comparing the original hippocampal output with that of the hippocampal output that has passed through the rhinal cortices. Future studies will have to combine multiple anterograde tracer injections, including ones which label only neurons 1 synapse removed and those which are able to jump multiple synapses. If fidelity the fidelity control hypothesis is correct, one would expect to see high levels of overlap between neurons in TE labeled by the different tracers.

The above view may lead to the false perception that extra-hippocampal (perirhinal and entorhinal) regions act as simple passive relays of information for processing by the hippocampus. However, as will be show in section 2.2, lesions of different regions within the MTL produce distinct behavioral deficits attesting to more active roles of these structures in the mnemonic process.

2.1.6 - Comparative Anatomy of the MTL

While at the gross anatomical level there are striking similarities in the general organization of the medial temporal lobe across the animal kingdom, there are

structural differences in the organization of the nervous system between rodents and primates. These have undoubtedly arisen because of selective evolutionary pressures, resulting in an emphasis on olfaction in the rodent and vision in the primate.

A major neuroanatomical difference between rodents and primates is the massive increase in the size of the neocortical mantle. In the rhesus macaque, nearly half of the cortical mantle is dedicated to unimodal visual processing, while the relative proportion in the rodent barely occupies one sixth of the cortex. Notably however, perirhinal and parahippocampal areas occupy approximately the same proportion of the cortical area in the monkey as in the rat. (Burwell et al., 1995). Perirhinal and postrhinal cortices of the rhesus macaque receive primarily visual type cortical inputs, while in the rodent inputs to these regions are distributed more evenly across all sensory modalities. Moreover, the patterns of intrinsic connectivity between the PH and PRC in the rodent are similarly organized to those of the rhesus monkey, suggesting that while there may exist differences in their inputs, the underlying computations performed within these regions are likely to be similar (Burwell et al., 1995).

The entorhinal cortex in the rhesus macaque is approximately a quarter of the size of the adjoining perirhinal and parahippocampal cortices, whereas in the rat the two structures are about the same size as the entorhinal cortex. At the cytoarchitectural level, the macaque entorhinal cortex is primarily distinguished from the rodents' by a distinctively more laminar appearance (Amaral et al., 1987). The rodent EC is generally divided into medial and lateral subdivisions, the monkey EC is divided into seven distinct

subregions. This subdivision of entorhinal cortex, in part, reflects the different sources of cortical input into the entorhinal cortex (Insausti et al., 1987b). The segregated nature of cortical inputs into the monkey entorhinal cortex is further reflected in the intrinsic connectivity between these subregions. Studies of intrinsic entorhinal projections demonstrates the existence of three functional segregated domains (Chrobak and Amaral, 2007; Mohedano-Moriano et al., 2007).

In contrast to the increased proportion of vision related structures in the primate brain, compared to the rodent brain, there occurred a relative weakening of olfactory related projections, although the general organization of these projections is preserved in rodent and primates (Carmichael et al., 1994). The EC is one of the few structures to receive direct projections from the olfactory bulb, which in the rodent preferentially innervates the lateral entorhinal cortex while the same projection in the macaque is restricted to a narrow caudal region (Insausti et al., 2002). This difference suggests that olfactory system in the primate has far less of an influence on information processing in the hippocampus than it does in the rodent.

At the level of the hippocampus, the two most striking differences are the increased thickness of the cell body layer in CA1 (~ 15 neurons wide vs. 5 neurons wide in the rodent), and the nearly complete absence of commissural connections between the two hippocampi. Notably, commissural projections between the subicular and entorhinal cortices appear to be as robust in the primate as in the rodent (Amaral and Lavenex, 2006).

Significant interspecies differences in cytoarchitecture and intrinsic connectivity are observed in the dentate gyrus. A subset of dentate granule cells in the monkey possesses an additional basal dendrite, which projects into the polymorphic layer (Seress and Mrzljak, 1987). *In vitro* examinations of these neurons reveal significant increases in postsynaptic currents following antidromic stimulation, suggesting that there is an enhanced element of recurrent excitation within the primate dentate gyrus (Austin and Buckmaster, 2004). Some researchers have suggested that along with the 50% decrease in interneuron to granule cell ratio in primates, these morphological differences may be a crucial element in the emergence of epileptiform activity (Seress and Ribak, 1992).

Mossy cells in the rhesus macaque tend to be of two types: the first appears much like the standard rodent mossy cell with dendrites in the polymorphic layer and axons that give rise to the associational-commissural connections that project to the inner molecular layer; A second type has arbors which extend into the molecular layer (where they may receive perforant path input), and also project heavily into the CA3 region (Buckmaster and Amaral, 2001), suggesting multiple paths of information flow to CA3 via the dentate gyrus.

2.2 Neuroanatomical Substrates for Recognition Memory in Rhesus Macaques

Among the earliest indications that MTL structures were involved in mnemonic processes came from the seminal work of Scoville and Milner (1957) who reported

dramatic anterograde and time limited retrograde amnesia in patient HM following a bilateral hippocampectomy. The anterograde component of his amnesia interfered only with his ability to form new declarative/episodic memories; skill learning was completely unaffected. While many studies had historically focused on observing behavioral deficits in primates following lesions to portions of IT cortex and beyond, it was the discovery of HM's specific deficits that served as a catalyst for nearly half a century of scientific investigation into the role of the medial temporal lobe in the mnemonic process (for an excellent historical review see Gross, 1994). Experimental attempts to quantify subregion specific contributions to mnemonic processes have employed a large arsenal of lesions including neurotoxic, electrolytic and aspiration, and temporary inactivation.

Mishikin and Delacour (1975) were among the first to examine mnemonic process in MTL lesioned animals by designing the now heavily used delayed non-matching-to-sample (**DNMS**) task. In this task, animals are presented with an item and, following a variable delay, are presented with a choice pair consisting of the original and a novel item. Animals must learn to respond to the novel item in order to obtain reward (Figure 2.6 A). The performance of a subject is assessed by determining the percent correct discrimination across different time delays. An additional test of visual recognition memory is the Visual Paired Comparison (**VPC**) task or Visual Preferential Looking Task (**VPLT**) (Figure 2.6 B), which takes advantage of an innate novelty preference shown by primates (Standing, 1973; Murray et al., 1976; Rose et al., 1982).

The most basic variant of VPC measures the amount of time an animal spends looking at a novel item versus a familiar item.

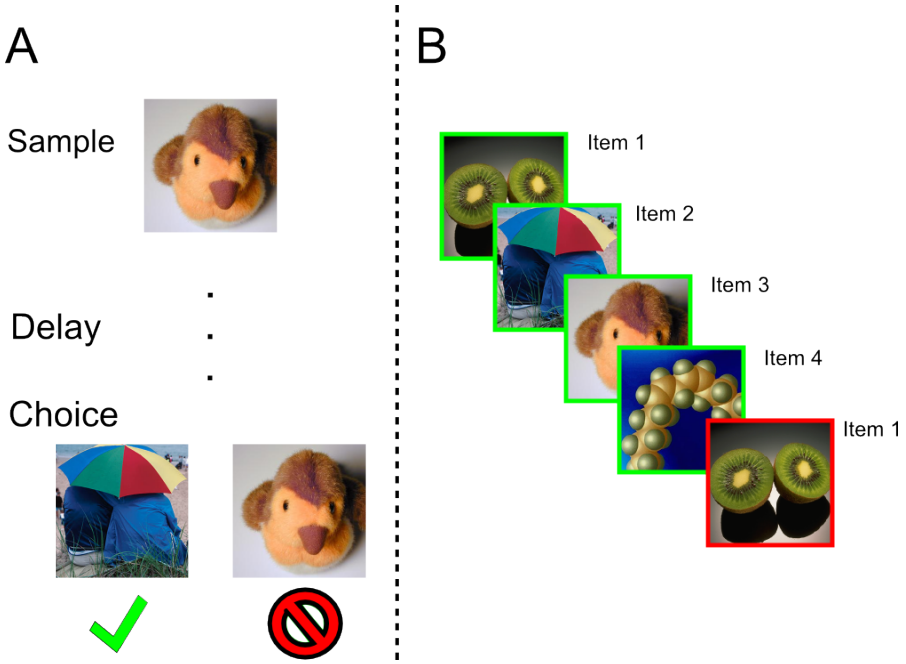


Figure 2.6 - Paradigms for studying recognition memory
A. Delayed Non-match-to-sample. Subjects are presented with a sample stimulus followed by a variable time delay ranging from seconds to minutes. After the time delay animals are presented with two choices. Performance is measured as the percentage of the total that an animal correctly chooses the novel image. **B. Visual Preferential Looking Task.** Animals are presented with a series of images. After a variable number of intervening images animals are shown a repeat image (Item 1). Behavioral variables of interest are % of time animals spend looking at the first and subsequent exposure to the image.

2.2.1 Cortical contributions to the mnemonic process

In contrast to lesions of the hippocampal formation that produce principally mnemonic (including visuo-spatial) impairments, lesions of other structures in the temporal lobe produce a more varied pattern of deficits that reveal those regions role in both mnemonic and perceptual processes. Beginning most laterally, lesions of area TE—the primary visual cortical input to PRC—produce a severe and lasting deficit for any

type of visual object recognition (e.g., Iwai and Mishkin, 1969; Huxlin et al., 2000; Buffalo et al., 2000). Specifically, animals with lesions to area TE show pronounced impairments on the DNMS task even at extremely short delays (500 msec), with some animals failing to acquire the task (Vogels et al., 1997; Buffalo et al., 2000). Human subjects with lesions to the inferior temporal cortex are often able to describe an object in great detail yet are left unable to name or recognize the object in question—classic hallmarks of visual agnsosia (Farah, 2004). These studies clearly support a role for area TE as a higher level visual area necessary for object recognition, but with only a marginal mnemonic role, as the majority of the observed mnemonic deficits arise from a perceptual deficit[3]. In contrast, PRC lesions produce a broad array of deficits across a variety of recognition memory tasks.

Initial indications of mnemonic deficits came from studies employing a DNMS paradigm, which found that animals were not only impaired in acquiring the DNMS rule but that performance accuracy was also significantly affected by the length of the delay between the sample and choice stimuli (Meunier et al., 1993). These impairments are independent of the sensory modality, as evidenced by impaired performance on tactual discrimination versions of the DNMS task (Suzuki et al., 1993).

The role of the perirhinal cortex in recognition memory performance began to assume a new dimension when Eacott et al. (1994) demonstrated that the impaired

[3] A full discussion of the perceptual deficits induced by TE lesions is beyond the scope of this document, for excellent reviews on the subject, as well as the physiology of the region see Miyashita (1993), as well as Tompa and Sáry (2010).

performance of animals with bilateral perirhinal/entorhinal lesions on a delay-match-to-sample (DMS) task is significantly affected when animals must learn a large set size in order to complete the task successfully. Performance on the large sets remained impaired even when the delay between sample and choice stimuli was reduced to 0 seconds. Strikingly, when experimenters introduced smaller sets of stimuli whose visual appearance was distinct (i.e., very low little similarity between them), performance improved and even equaled that of unoperated controls when animals only had to learn two stimuli. The observation of impaired performance in the absence of any retention demands (0 sec delay) and that DMS performance could be rescued by making stimuli more easily discriminated suggested that the deficits of animals with PRC lesions extended beyond the mnemonic domain and that they may be more broadly related to deficits in making judgments about stimulus identity.

Subsequent to the finding of Eacott et al. (1994), Buckley and Gaffan (1998) demonstrated that macaques with PRC lesions are significantly impaired in both the identification of previously learned objects presented in a rotated view, as well as familiar objects presented in scenes—adding further support to the hypothesis that lesions in this area produce perceptual deficits. In a more direct test of this hypothesis, Buckley et al. (2001) specifically designed a perceptual oddity task that required animals to indicate via touch screen which stimulus out of a simultaneously displayed set is different from the others. Animals were able to readily discriminate stimuli when the dimensions to be differentiated were color, shape or size, even when differences

between these stimuli were only very minor. However, when animals could not use overt features (e.g., color, etc.) but instead had to base their judgments on more complex features of the stimuli, PRC lesioned animals were significantly impaired. Similarly, Bussey et al. (2002), systematically varied the perceptual ambiguity between four concurrently presented stimuli. Animals with aspiration lesions to the PRC were increasingly impaired (quantified as errors to criterion on the discrimination problem) as perceptual ambiguity between the stimuli increased (Figure 2.7). More recently, similar perceptual deficits have been demonstrated in rodents (e.g., Norman and Eacott, 2004; Bartko et al., 2007) and humans (e.g., Barense et al., 2005).

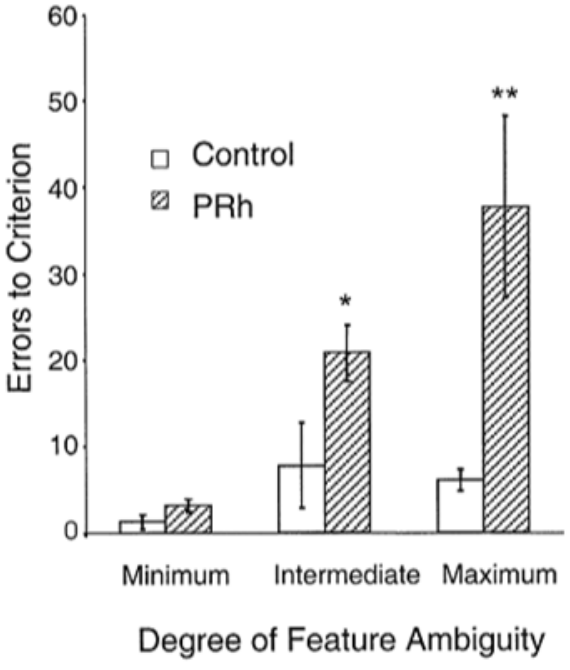


Figure 2.7 - Perirhinal lesions impair perceptual discrimination
To determine whether perirhinal cortex is involved in making perceptual judgments animals Bussey et al., (2002) designed a perceptual discrimination task with 3 levels of ambiguity between two simultaneously visual stimuli (minimum, intermediate and maximum). Animals were required to select one of two stimuli. Animals with PRC lesions showed a large increase in

the number of errors made in the intermediate and maximum ambiguity conditions. Control (n=4), unoperated controls, PRh (n=4) bilateral perirhinal lesions. From (Bussey et al., 2002)

In addition to the deficits described above, animals with PRC lesions have also been shown to be significantly impaired on tasks requiring the formation of stimulus-stimulus associations. At their root, stimulus or conditional associations require animals to make a series of associations between two arbitrary stimuli, and learn to use these to guide their behavior. Animals performing traditional paired associate tasks are presented with a stimulus A followed by a stimulus B, which requires the animal to make a behavioral response to receive reward. When stimulus C follows stimulus A, this requires that the animal withhold its response in order to receive reward (e.g., Murray et al., 1993; Higuchi and Miyashita, 1996). Lesions to the MTL, and specifically the PRC, produce a severe deficit in the ability of animals to rapidly acquire configural and paired-associate tasks of this nature (Murray and Gaffan, 1994; Bunsey and Eichenbaum, 1995; Buckley and Gaffan, 1998).

Similar to deficits in visual associative tasks, trace and delay conditioning tasks provide a further view into the role PRC in the acquisition of associative memory. Delay conditioning relies on animals learning the simple associations between a conditioned stimulus (CS) (e.g., a tone or light) with a temporally overlapping unconditioned stimulus (US) (e.g., electric shock, air puff, or a very loud tone), while during trace conditioning experiments there is no temporal overlap between the two stimuli. In both paradigms, animals eventually associate the appearance of the CS with the US, such that the presentation of the CS alone elicits the response (e.g., startle) associated with the US.

Rodents with lesions of the PRC are unimpaired at acquiring CS-US discriminations, in both trace and delay versions, when the CS is simple such as a continuous tone. However, when the CS stimulus is complex, such as ultrasonic vocalization (**USV**), or the CS is associated with a spatial context, rodents with PRC lesions are severely impaired (Kholodar-Smith et al., 2008a, 2008b).

Taken together these studies suggest two views of PRC, one in which the PRC is responsible for perceptual discrimination of complex stimuli and another in which PRC is involved in building associations between different stimuli, including across different sensory modalities. These two, seemingly different, cognitive demands can be reconciled under a general model of PRC function, in which PRC acts to construct a unified representation of complex stimuli by linking neural representations located in different cortical areas. Specifically, in the case of the perceptual discrimination problems, when the stimuli to be discriminated can easily be distinguished by overt features such as color or shape (on which animals with PRC lesions are not impaired), the discrimination problem can be easily solved by lower level visual areas. However, when the stimuli to be discriminated are highly similar or contain a large number of overlapping features, subjects must use a full, or unitized, representation of the stimulus to solve the problem. This view, first formalized by Murray and Bussey (1999) and often referred to as the "perceptual-mnemonic feature conjunctive model" has received significant support from theoretical studies (Bussey and Saksida, 2002) and electrophysiological data (section 2.3.1). Finally, the lesion and behavioral data

presented above suggests that previous accounts of a functionally segregated “medial temporal lobe memory system” may be incomplete.

In contrast to other MTL structures, the entorhinal cortex (EC) has received relatively little attention. An early study, which examined the relative contribution of PRC vs. EC to DNMS performance, found only very minor impairments in the ability of EC lesioned animals on the DNMS task. EC lesioned animals, on average require 100 trials to relearn the DNMS task following surgery, while PRC lesioned animals require nearly 400 and commit significantly more errors. Similarly, the performance on different temporal delays for EC lesioned animals is only marginally different from unoperated controls (Meunier et al., 1993; Buckmaster et al., 2004). However, when animals are tested on tasks requiring generalization of previously learned conditional associations such as paired associate (Calkins, 1894; Thorndike, 1908) or transitive inference (Burt, 1919; McGonigle and Chalmers, 1977), EC lesioned animals show significant impairment relative to controls. For instance, in transitive inference tasks, animals learn a series of stimulus associations (e.g., A+B- B+C-, C+D-, D+E-, in which +/- indicate positive or negative reward respectively) and are subsequently tested on novel, indirectly related items (i.e. B+D or C+A) in which animals must choose B over D, in accordance with the hierarchical nature of the initially learned associations. Specifically, EC lesioned animals readily acquire individual associations, but are severely impaired on responding to novel configurations.

2.2.2 Mnemonic deficits following lesions to the hippocampal formation

A key observation in the mnemonic deficit of HM (and other patients) was the appearance of a temporally limited retrograde amnesia as well as a profound anterograde amnesia. In the case of HM, his memory of temporally remote events were intact but his recollection of persons or events encountered shortly before (a few weeks) the surgery was significantly impaired. Similarly, MTL and hippocampal lesions in primates produce similar temporally graded deficits, with animals exhibiting amnesia up to four weeks prior to surgery (Zola-Morgan and Squire, 1990). However, when animals receive an additional lesion of the underlying cortical structures, the temporal extent was significantly extended (Murray et al., 1993). These findings have been interpreted to suggest that the hippocampus may facilitate the encoding of memory in the cortex and that after some time delay, these memories (colloquially referred to as “traces”) become independent of the hippocampus.

The anterograde component of the effects of MTL lesions is most commonly observed as pronounced performance deficits on recognition memory tasks such as the DNMS or VPC. Selective ablation or inactivation of the hippocampal formation produces a variety of results most consistently pointing in the direction of preserved memory at short temporal delays but with increasing difficulties at longer delays (> 10 minutes; (Alvarez et al., 1995; Beason-Held et al., 1999; Zola et al., 2000; Heuer and Bachevalier, 2011). Interestingly, when animals receive intensive pre-training on the DNMS task, HC lesioned animals are similar to unoperated controls (Murray and Mishkin, 1998).

However, pre-trained animals that received rhinal lesions (discussed above) are significantly impaired on the same task. These data are consistent with the idea that hippocampal damage impairs the ability of subjects to rapidly form new memories, especially when new memories require certain types of relational learning or significant temporal delays. Moreover, these data suggest that extensive pre-training can mitigate deficits associated with hippocampal lesions. Specifically, it may be possible that pre-training on the DNMS task alters the circuitry of the PRC in such a way to allow the PRC to solve the task independent of the hippocampus.

Zeamer et al. (2011) expanded on the issues raised by the Baxter and Murray (2001) meta-analysis, by noting that in several studies included in the Baxter meta-analysis there were crucial differences in the experimental stimuli used. In most cases, studies using DNMS tasks used actual objects, while VPC experiments used projected images which were matched for luminance and size. This led to the hypothesis that perhaps HC lesioned animals were impaired in discriminating between objects that were visually similar, and that the deficits on the VPC task were not due to a mnemonic deficit but rather were due to the nature of the experimental stimuli used. By varying the encoding time and stimulus similarity, Zeamer et al., (2011) were able to demonstrate that performance on a VPC task was intact for dissimilar objects but became significantly impaired as stimuli became more similar (Figure 2.8). In addition, deficits were much more pronounced when the encoding time was varied such that the less time animals had to look at the image, the worse their performance became. The deficit

in VPC for highly similar items suggests that one function of the hippocampal formation is to act as a "comparator", which rapidly disambiguates items which are highly similar (Vinogradova, 2001). The sensitivity of encoding time on performance of the VPC task suggests that structures upstream of the hippocampus like the perirhinal cortex are able to compensate for the deficit in visual recognition memory when sufficient encoding time is provided.

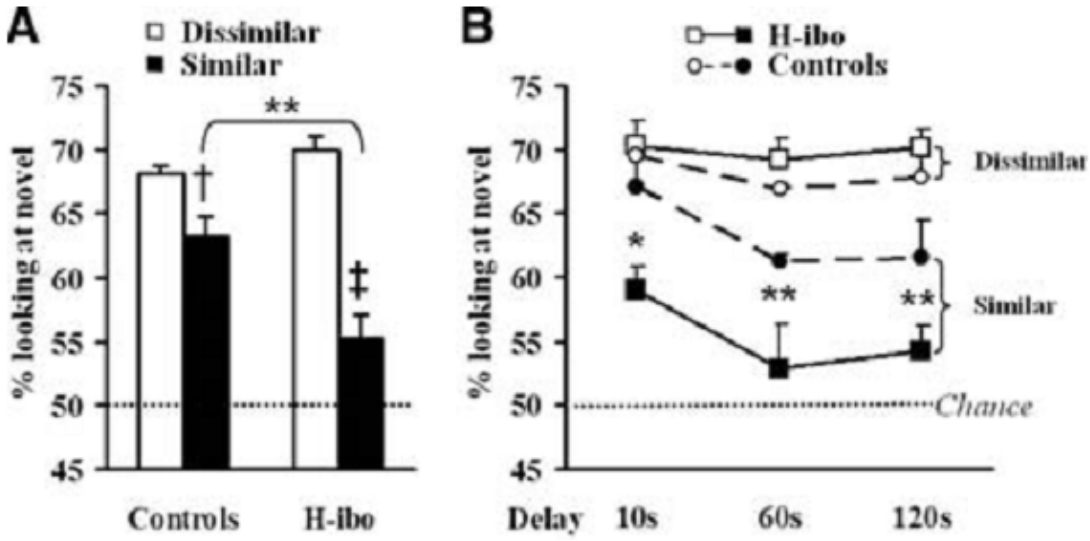


Figure 2.8 - Hippocampus dependent changes in novelty preference
Animals were presented with either high similar or high dissimilar images in a VPC task similar to figure 2.5B. In the VPC task animals are presented with an initial familiarization image and are then shown a second image (which in this case may or may not be very similar). Responses are measured as % looking time at novel images. **A. Averages across all delays.** Hippocampal lesioned animals accurately discriminate between the two images when images are dissimilar. However when images are highly similar lesioned animals spend less time exploring novel images, indicating a failure to disambiguate the two images. **B. Temporal Delays.** As in (A) but expanded across the range of temporal delays. From (Zeamer et al., 2011).

In addition to recognition memory deficits, lesions of the hippocampus in both primates (Murray et al., 1998) and rodents (for review see: Barnes ,1988) can produce

severe impairments in spatial and spatial relational learning. Banta Lavenex et al. (2006) demonstrated that in the absence of local cues, freely-moving hippocampal lesioned animals are unable to utilize allocentric spatial representations to determine the location of a food reward. These spatial recognition memory deficits extend through to delayed match (Hampton et al., 2004) and non-match (Alvarado and Bachevalier, 2005) to location tasks. These results are in line with electrophysiological data in freely behaving rodents (Wilson and McNaughton, 1993a), restrained primates (Rolls et al., 2005), and virtual reality in humans (Ekstrom et al., 2003), demonstrating exceptional sensitivity of hippocampal pyramidal cells to spatial locations. Notably, in experiments involving spatial learning, lesion size is positively correlated with behavior on a spatial relation task such that the best performing animals exhibit the smallest lesions, a finding which highlights the importance of the hippocampus in tasks with spatial components (e.g., Moser et al., 1993; Broadbent et al., 2004).

However, experiments employing a reduced object-in-place task (primarily to test episodic memory), are more ambiguous with respect to hippocampal involvement, with both support for (Parkinson et al., 1988; Murray et al., 1998; Malkova and Mishkin, 2003) and against (Banta Lavenex et al., 2006) a causal role. Object-in-place tasks require animals to recall the correct object as well as its position on a board (Parkinson et al., 1988), and it may be argued that the ambiguity of the data arises in part from the relatively minimal spatial component of these tasks. In fact, episodic memory in humans is typically formed in much larger environments, begging the question of whether the

spatial demands of these reduced tasks truly require the hippocampal formation, or whether structures outside of the hippocampus may be able to compensate for its absence. Taken as a whole, the data from hippocampal lesioned rhesus macaques point to several interrelated functions of the hippocampal formation:

1) The hippocampus may facilitate the rapid acquisition and consolidation of memories in the neocortex (e.g., Zola-Morgan and Squire, 1990; Murray et al., 1998).
2) The hippocampus acts as comparator of incoming information, thereby disambiguating between different memories, and is thereby possibly able to detect novelty (McNaughton and Morris, 1987b; Vinogradova, 2001; Zeamer et al., 2011).
3) The hippocampus is involved in the construction of allocentrically based spatial associations (e.g., O'Keefe and Nadel, 1978; Rolls et al., 1989; Banta Lavenex et al., 2006).

While there has been a tremendous advance in determining the contribution of the hippocampal formation to the mnemonic process, several questions remain. Recent work by Zeamer et al. (2011) and the meta-analysis by Baxter and Murray (2001) suggest that more careful attention needs to be paid to the stimulus type as well as the amount of time animals have to "encode" a particular stimulus. Moreover, it remains unclear what the subregion-specific contributions to the mnemonic process are. For example, using transgenic mice, Nakashiba et al. (2008) were able to show that a

selective knockdown of NMDAr activity at CA3/CA1 synapses spared multi-trial spatial reference memory scores while producing a deficit in a single trial fear conditioning paradigm. These results suggest that when multiple trials are involved, the direct EC/CA1 pathway is sufficient, but that rapid learning requires the integrity of the Schaffer collateral pathway.

2.2.3 Conclusion – Integrative Hierarchy of Processing

Half a century of research clearly implicates medial temporal lobe structures in both object recognition memory and episodic memory, as evidenced by lesions across multiple species. More recently, a series of studies have demonstrated that lesions across the MTL can produce significant problems in perceptual discrimination, prompting reconsideration of the historical data. The assignment of a specific function to particular subregions has been further complicated by a host of experimental issues. Forming a consensus across studies is difficult due to the tremendous experimental variation in: **1)** lesion size (in some studies as much as 50% of a region was spared); **2)** the lesion method (aspiration lesions damage passing fiber bundles vs. neurotoxic which spares these fibers); **3)** subtle behavioral factors (differences in performance between the use of actual objects versus projected images); **4)** the variable range in amount of time an animal has to examine a stimulus; **5)** whether animals are trained pre/post-operatively (Murray and Bussey, 2001; Baxter, 2009).

In spite of these difficulties, the emerging view is not one that sees the MTL as a unitary structure dedicated solely to mnemonic functions. Rather it may be more useful

to think of the MTL as a hierarchical system that supports the acquisition and abstraction of relevant relationships—be they spatial, sensory, or temporal—between items and events in an organism's environment. As a consequence, the hippocampus is able to support both perceptual and mnemonic processes simultaneously. This highly specialized function is further underscored by lesion data from infant primates. When infants receive bilateral lesions of area TE at 10 months, they show relatively spared learning and re-learning of the DNMS task (with exception of delays > 60 sec), while damage to MTL (Hippocampus, EC, and PRC, and Amygdala) produced a permanent impairment on even simple visual object recognition tasks (Bachevalier and Mishkin, 1994). These results highlight the remarkable efficacy by which a deficit in a higher level visual association area can be compensated for, but also that compensation to MTL structures is extremely limited (if not entirely absent), suggesting that the intrinsic and extrinsic circuits (and the computational functions instantiated by them) are highly specialized and cannot be readily recapitulated by other neocortical networks.

2.3 Neural Encoding

The preceding review of the anatomical and behavioral data clearly implicates MTL regions as playing active roles in both mnemonic and perceptual processes. The advent of invasive single unit recording technologies has begun to reveal how individual neurons contribute to the encoding of memories and how this activity relates to the learning process. The following section will review in turn the current state of

knowledge regarding visual and mnemonic processes in the cortical and hippocampal regions of the medial temporal lobe.

Before beginning this review it is important to note that early studies of the higher level visual association cortices focused broadly on the inferior temporal (IT) region. More modern anatomical techniques now indicate that IT cortex is subdivided into many functionally distinct regions. Unfortunately, there has been a relative dearth of studies which have focused on examining the response properties of single neurons restricted specifically to these regions. For this reason, much of the physiology data regarding cortical regions is discussed in a broader context of IT cortex, which can include TE, TEo, TEa and even PRC (for review of the history of the nomenclature of regions in the IT cortex and MTL see: Suzuki and Amaral (2003b) . Similarly, owing to the difficulty in precisely targeting deep subcortical structures in primates, anatomical information of recordings from the hippocampal regions of primates is often incomplete and sometimes combined for analysis purposes. Lastly, given the focus of this dissertation, as well as for sake of brevity, the weight of the discussion will fall primarily on data from studies involving primates, rather than rodents (although rodent findings will be discussed where appropriate or data from primates is lacking).

2.3.1 Mnemonic properties of Perirhinal Neurons

Perirhinal cortex (PRC, areas 35/36) primary afferent input arises from neurons in area TE (Saleem and Tanaka, 1996); however to date, there has been no concerted effort to determine what differences exist in the stimulus selectivity or specificity of

neurons in PRC or TE. Moreover, while neuronal responses in TE tend to show clear cortical organization with nearby neurons having similar stimulus selectivity (e.g., faces), it is unclear whether PRC shows similar organization, though in general the data do not support this view. However, some general statements regarding the stimulus selectivity of neurons in these regions can be made.

Neurons across regions formerly defined as IT Cortex respond almost exclusively to visual stimulation and are more responsive to complex images than to generalities (color or shape of presented objects). Experimental estimates of how many neurons are visually responsive (including inhibited responses) vary widely from ~30% - 80% (Fuster and Jervey, 1981; Gross, 1992; Rodman et al., 1993; Desimone, 1996; Xiang and Brown, 1998; Hölscher et al., 2003). Individual neurons are broadly tuned, giving at least some response to almost any given image independent of stimulus categories (e.g., animal, person, object). These responses suggests that IT cortex utilizes a highly distributed population code to store information (Desimone et al., 1984; Baylis et al., 1985), implying that the representation of a stimulus (e.g. an image) at the neuron level is supported by the activity of many neurons. As a population, IT neurons are selective across a range of items, including hands, faces, and computer generated objects, and other “complex visual stimuli” (Miyashita, 1993; Erickson and Desimone, 1999; Mormann et al., 2008). Neural responses to an image are completely invariant with respect to size, luminance, and location, suggesting that these neurons form a highly

abstracted and cohesive representation of an object (Miyashita, 1993; Booth and Rolls, 1998).

The broadly-tuned visual responses of inferior temporal cortex neurons, coupled with the observation that the average human may recognize on the order of ~10,000 – 30,000 objects (Biederman, 1987), underscores the mystery of how the brain manages to efficiently represent this vast number of stimuli without regularly misclassifying objects. Theoretical proposals have advanced the hypothesis that one mechanism by which neural networks can maintain encoding efficiency is through a tuning process. Simply stated, these proposals suggest that modification of the number of stimuli that a given neuron responds to reduces the possibility of overlap between representations in the population (e.g., Marr, 1971; McNaughton and Morris, 1987a; Zhang and Sejnowski, 1999; Pouget et al., 1999). While experimental data generally support the use of distributed codes as envisioned by these theories, the evidence for experience-dependent tuning is equivocal and in some cases points towards a broader tuning following learning (Kobatake et al., 1998), while overtraining on parts of objects or category learning appears to induce narrower tuning (Baker et al., 2002; Freedman et al., 2006). While neurons across the IT cortex were often studied in relation to visual perception, neurons in the PRC specifically were often the studied in relation to mnemonic processes.

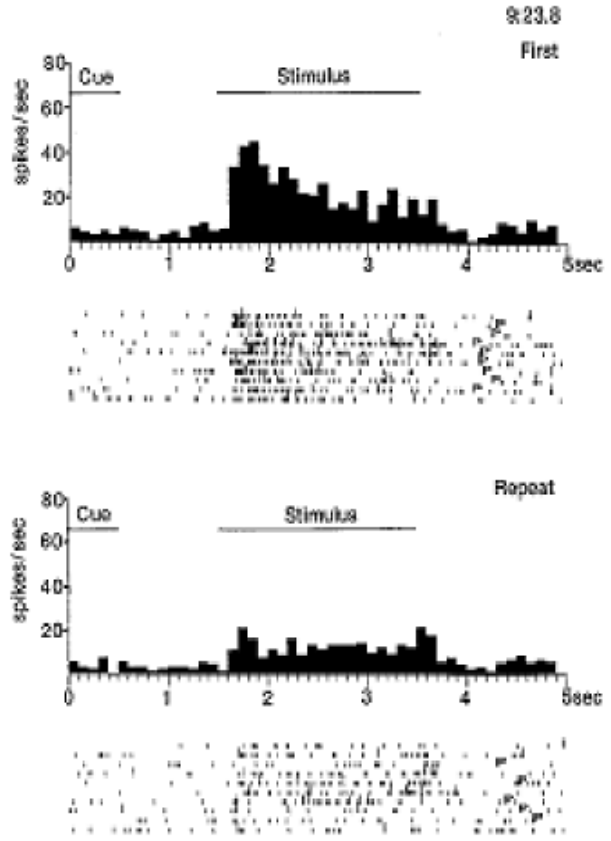


Figure 2.9 - Response Decrement in PRC neuron
Spike raster and associated firing rate histogram for one perirhinal neuron. Each line in the spike raster represents the spiking response of this neuron to one image, in this case 10 images. Spike rate histogram represents the averaged spiking response across all 10 responses. Top panel shows this neuron's response to the first presentation of an image while the bottom panel shows the repeat exposure of the same image. Note reduced firing rate for repeated stimulus presentations. From Fahy et al., (1993)

Early studies on the response properties of PRC neurons in behaving rhesus macaques found an experience-dependent decrease in firing rate of neurons to an image that the neuron was selective for (Brown et al., 1987; Riches et al., 1991; Fahy et al., 1993; Vogels et al., 1995; Xiang and Brown, 1998, Figure 2.9). More specifically, across a variety of tasks, many neurons (approximately 40%) in the PRC show a reduced firing rate when comparing the firing rate of the first presentation of an image to that of

the second presentation of the same image (Miller et al., 1993). The decreased response magnitude persists across many intervening stimuli, even up to 24 hours later (Xiang and Brown, 1998). However, several studies have also reported increases in firing rates to repeated stimulus presentations both during short (Gross, 1992) and long (Hölscher et al., 2003) intervals between stimulus repetitions. The observed decrements in the activity of single neurons has been suggested to reflect the relative familiarity (or recency) of a stimulus, and thus the serve as the cellular foundation for recognition memory (Riches et al., 1991; Xiang and Brown, 1998).

A crucial test of the hypothesis that a response decrement in neurons subserves recognition memory would be an experimental preparation, which demonstrates that an absence of response decrement impairs familiarity judgments. Miller and Desimone (1993) tested this hypothesis by injecting the cholinergic antagonist scopolamine into TE and simultaneously recording the activity of single units in the primate inferior temporal cortex. Their results showed a clear reduction in accuracy on a recognition memory task; however, there was no change in the responses of neurons to the stimuli. Similarly, Sobotka and Ringo (1996), using a partial split brain preparation, which left only the anterior commissure intact, showed that when images are presented to the eye ipsilateral to the recording site, recognition performance was > 95% correct and neurons showed the expected response decrement. However, when the stimuli were presented to the contralateral eye, performance stayed high (~86% correct), but the previously observed decrement of firing rates of inferior temporal cortex neurons did

not occur. Moreover, the decrements have also been observed when the stimuli are completely irrelevant to an animal (Vogels et al., 1995), and even when animals are deeply anaesthetized (Miller et al., 1991a).

A series of imaging studies using the immediate early gene (IEG) c-fos were conducted to further examine the relationship between response decrements and recognition memory (Zhu et al., 1997; Wan et al., 1999). Neurons produce c-fos in an activity dependent manner which can be utilized to visualize the responses of a large population of neurons in a behavioral task within a brain region. Specifically the Brown group attempted to reproduce the observation of a response decrement at the population level by selectively displaying either novel or familiar images to one eye at a time (hence one hemisphere at a time). The results revealed that PRC neurons in the hemisphere which received novel images showed higher number of neurons expressing c-fos than the hemisphere which "saw" only familiar images.

Similar to electrophysiological studies, many of the immediate early gene studies are significantly confounded at multiple levels. First, c-fos as a marker for activity is problematic as it is also expressed by glial cells (Edling et al., 2007). Consequently, in the absence of additional neuron specific markers it is impossible to assess whether these counts accurately represent neuronal activation. In addition, the interpretation of their results ignores fundamental principles of gene expression. Specifically, as c-fos is expressed in an activity dependent manner and the activity of the neurons in question is not turned off but only reduced, one would not expect fewer neurons to be positive for

c-fos. A response decrement would manifest itself at the level of amount of gene product. Quantifying a reduction in gene product is generally not accessible to gross immunohistochemical assays instead requiring highly sensitive PCR reactions. There are no studies that examine these claimed differences using PCR. Lastly, more rigorous studies using the immediate early gene Arc in a similar recognition paradigm failed to replicate the effects found by the Brown group (Burke personal communication).

Interestingly, it should be noted that recent data from human imaging studies have found that the haemodynamic response decrement often observed in fMRI does not occur when 3D objects are instead of 2D objects are shown (Snow et al., 2011). So while the observed decrementing responses of neurons in the inferior temporal cortex (including perirhinal cortex) provide a compelling story, a more careful reading of the literature does not support a role for these changes in the recognition memory process.

Lesions of area 35/36 (PRC) produce a wide spectrum of deficits across visual mnemonic tasks, with more recent data indicating that these deficits may be tied to a perceptual deficit. The observation of perceptual deficits following PRC lesions suggested that PRC sits at the top of a processing hierarchy and that one of its major functions is to associate different stimuli, which are represented discretely in lower cortical areas so as to construct a “unitized” representation supporting visual association memory (Barlow, 1961; Murray and Bussey, 1999). The construction of unitized representations has been proposed to be related to an animal’s ability to acquire visual paired-associate tasks (Buckley et al., 2001).

IT neurons (both in TE and PRC) show an experience-dependent modification during paired associate tasks in their responses, such that neurons that were previously only selective to one of the items developed a response to the paired stimulus (Miyashita, 1988; Sakai and Miyashita, 1991). Paired associate learning, and the corresponding responses observed in posterior IT Cortex (TE) are completely absent following lesioning of the EC and PRC—underscoring the role of the PRC in driving the development of associative learning (Higuchi and Miyashita, 1996). In a modified paradigm, Erickson and Desimone (1999) found that individual neurons exhibited elevated firing rates during the delay-period and that the magnitude of this activity was significantly correlated to the magnitude of the visual responses to both the first and second stimulus. Critically, there was no correlation between delay period activity and responses to the second stimulus for novel images, indicating that the correlation to the second stimulus only gradually developed as a function of experience. It has been hypothesized that delay period activity in perirhinal neurons forms a quasi-retrospective representation of the first stimulus and that this activity is then used to "link" the first and the second stimulus.

If the theory of hierarchical processing and the "unitization" of representations is correct, then there should exist measurable differences between TE and perirhinal regions A36 and A35. One prediction of this hypothesis is that at the final level of association, neurons should no longer show differences in the selectivity between the optimal cue and its paired associate. Given the technical challenges of targeting the

relatively small area 35 of the PRC most studies have focused on recording from area 36 instead. To examine whether there were differences between these regions Fujimichi et al., (2010) used high resolution MRIs to selectively target recoding electrodes and to record the responses of single neurons in both regions. As expected, neurons with delay period activity in both regions showed enhanced correlations between the cue and its paired associate. Consistent with previous experiments, experience on a paired associate task produced enhanced correlations to either cue or the paired associate during the delay period in both regions. However, in contrast to area 36 neurons, the delay period activity of neurons in area 35 no longer discriminated between the cue and its paired associate (Figure 2.10). Importantly, these neurons retained the ability to discriminate between the different pairs.

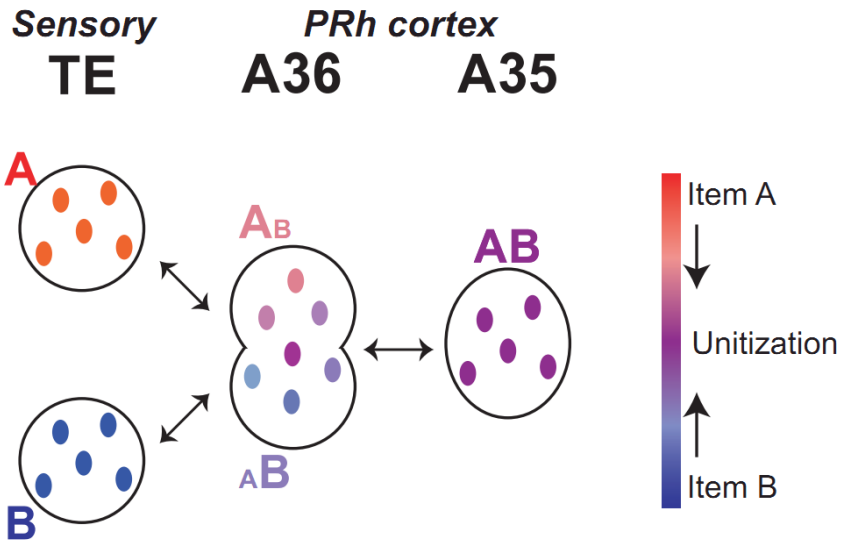


Figure 2.10 - Hierarchical processing underlying item unitization in medial temporal lobe
A subject is presented with two items A and B as part of a paired associated task. Area TE (unimodal visual sensory) represents A and B in separate non-overlapping populations of neurons. The responses of neurons in area 36 indicate that here, neurons respond to some

common elements of the conjunction between A and B, but the magnitude of the response still differentiates between the two images. In area 35 neurons respond to both items equally, indicating that paired associates are encoded as a unitized item (purple). From (Fujimichi et al., 2010)

The paired response data suggest that at this level neurons represent only the conjunction and not to its components, adding compelling evidence in support of the perceptual-mnemonic theory of PRC function and pointing towards an anatomical region where perception becomes memory. To further understand how these neurons undergo experience-dependent modification requires an examination of the underlying plasticity mechanisms, which provide the final dimension to our understanding the PRC function. Unfortunately (and understandably), there are no *in vitro* electrophysiological studies of primate IT Cortex; consequently, the following discussion will focus primarily on data from rodents.

Modification of the synaptic contacts between neurons is widely believed to be critical for learning. Experimentally, changes in synaptic plasticity can be induced via electrical or pharmacological manipulation, resulting in the expression of long-term potentiation (LTP) and/or depression (LTD) (Malenka and Bear, 2004). Changes similar to those observed following experimental induction of LTP/LTD have been demonstrated to occur after learning in rats (Whitlock et al., 2006), providing an important link between these experimental phenomena and the biological phenomenon of memory. Importantly, there must always exist a balance between potentiating and depressing responses to ensure sufficient network storage.

In the perirhinal cortex, LTP can be induced in Layers II/III via relatively low intensity electrical tetanization of fibers (Bilkey, 1996). The observed enhancements of activity show associative specificity such that pairing of a strong stimulus in one electrode with a weak stimulus in a second electrode results in a significant enhancement of LTP when tested with just the weak electrode. Potentiation in the PRC is pathway specific and can occur both when stimulated via entorhinal or cortical inputs, further demonstrating the specificity of the enhancement (Bilkey, 1996). Several studies have also pointed towards the existence of LTD in PRC and that crucial features (specificity and associativity) are shared with LTP. Similar to LTP, LTD in the PRC is also dependent on NMDA receptors and is driven primarily via NMDAr internalization (Massey et al., 2008). Interfering with this internalization by blocking the interaction between the GluR2 subunit and the clathrin adapter protein AP2 results in a marked decrease in the expression of LTD, and when injected directly into the PRC of behaving animals, produces a significant deficit in visual recognition memory (Griffiths et al., 2008a).

As discussed previously, response decrements in a subgroup of PRC neurons has been suggested to be a possible mechanism underlying recognition memory. These observations led to the hypothesis that since recognition memory is associated with response decrements, these must be driven by an LTD-like process. Application of the cholinergic antagonist scopolamine in rodent PRC slices results in significantly reduced expression of LTD, but not LTP (Warburton et al., 2003). Moreover, visual recognition

memory in both primates and rodents is sensitive to cholinergic challenge (Miller and Desimone, 1993; Warburton et al., 2003; Turchi et al., 2005). Given the observed deficits in visual recognition memory the authors argue for a direct correlation between recognition memory, response decrements and LTD. Further examination however does not support this conclusion.

While scopolamine does disrupt visual recognition memory in primates, it does not alter the expression of response decrements (Miller and Desimone, 1993). In addition, while response decrements have been described in rodents (including anaesthetized animals) (Zhu et al., 1995, 1997), no studies exist directly demonstrating that scopolamine in rodents results in changes in response decrements. Moreover, recent studies using ethologically relevant behaviors and sophisticated high density multiple single unit recordings fail to find response decrements in rodent PRC (Burke personal communication).

In conclusion, while both LTP and LTD-like processes appear to be involved in the function of perirhinal cortex, they are unlikely responsible for driving response decrements. The question of how cellular processes related to plasticity mechanism are reflected in the dynamics of population of neurons and what the implications for neural encoding are will be addressed in both chapters four and five.

2.3.2 Hippocampal physiology: a synthesis of object and place

Deficits in episodic memory are a hallmark of hippocampal dysfunction and pathology (Scoville and Milner, 1957; Zola-Morgan et al., 1986). Episodic memory may be broadly considered as the integration of spatial information with information pertaining to features of the environments (e.g., persons, objects, time, etc), in other words association of a spatial context with additional features of the environment (Nadel et al., 2003). Mechanistically, the ability of the hippocampus to produce episodic memories has been associated with its capacity to **1)** rapidly acquire associations present in an environment and **2)** create an index code. Briefly stated, the "hippocampal index theory" posits that the hippocampus rapidly acquires information about an episode and stores this information locally as a pattern of activity across the population of hippocampal neurons (Teyler and DiScenna, 1986). Owing to the reciprocal connectivity of the hippocampus with its cortical afferents in the MTL, this local representation then serves as an *index* representing the pattern of cortical activity that is active during a particular episode. Two predictions of this theory are: 1) the partial activation of this representation can lead to the recall of the entire memory (e.g., a particular scent may recall a particular life experience) and 2) that continuous reactivation of a pattern of activity via the hippocampal index leads to a gradual strengthening of the association between anatomically disparate cortical connections. As indicated, the latter of these predictions has been suggested to explain the temporal

gradient of retrograde amnesia sometimes observed in patients with hippocampal damage.

Even though no conclusive data exist supporting or refuting these hypotheses, the last couple of decades have seen tremendous advances in our understanding of the physiology of the primate hippocampal formation. The following section will discuss the results from these findings in relation to hypothesized cognitive functions of the hippocampus. It should be noted that a critical shortcoming of many studies of hippocampal function in primates is the lack of accurate anatomical data that confirm the location of cells recorded. Moreover, in many cases where anatomical data are available, there are often insufficient neurons recorded from one region to enable statistical significance testing, and thus neurons from multiple regions are combined. Given the differences in intrinsic and extrinsic connections between different hippocampal subfields the results discussed below should be regarded in this context.

In contrast to the inferior temporal cortex, the response properties of hippocampal neurons are more heterogeneous. In primates, hippocampal neurons tend to be sensitive to visual stimuli, mnemonic activity, context, and spatial locations; they also respond to conjunctions between these factors. The following section will examine these response types in turn.

2.3.4 Representation and memory in hippocampal neurons

As is the case for studies of IT cortex, tasks used to probe the mnemonic function of hippocampal neurons are almost universally visual in nature. Hippocampal neurons

are responsive to a wide range of visual stimuli (e.g.,. scenes, objects, fractals), though experimental estimates of the number of neurons showing visual sensitivity varies widely from 5-60% (Xiang and Brown, 1998; Wirth et al., 2003; Yanike et al., 2004; Jutras and Buffalo, 2010). In contrast to neurons in upstream cortical regions (i.e., IT and PRC), individual neurons tend to be much sparser in that they respond to a smaller percentage of presented images. Approximately 20% of visually responsive neurons in the hippocampus are further sensitive to the category of visual stimulus (e.g., people, color, etc.), and the activity of these neurons on a delayed match to sample task reflects both errors in responding (i.e., selecting the wrong response based on category "person" rather than "color") as well as an animal's behavioral strategy (e.g., match based on similar color, Hampson et al., 2004; Quiroga et al., 2005).

Similar to recordings from IT cortex, a subset of hippocampal neurons are modulated by the relative familiarity or novelty of a given visual image. Responses tend to be heterogeneous, with some neurons showing a higher firing rate for novel images, while others show the opposite pattern (Jutras and Buffalo, 2010a). Crucially, there exists a strong positive correlation between the normalized difference in firing rates between novel and repeated images and the respective percent change in an animal's looking times. Hippocampal neurons have been shown to undergo changes in selectivity (measured as the firing rate differences between best and worst responses), akin to neurons in IT cortex, following learning of an association (Wirth et al., 2003). However, this study found both enhanced and decreased selectivity across the population of

neurons exhibiting this phenomenon, making it unclear how this could improve the ability for a network to discriminate visual stimuli. Moreover, the "selectivity index" measure is a simple ratio measure and describes the normalized difference between the "best" and the "worst" responses within a set of images, and does not accurately reflect whether the number of images a neuron is responsive to has changed (see chapter four for further discussion).

In addition to purely visual recognition studies, a number of studies have examined the responses of hippocampal neurons when animals must learn visual-motor associations such that the presentation of a specific scene or object signals a saccade direction (e.g., image of gorilla, saccade left) (Wirth et al., 2003). Approximately 60% of neurons were identified as scene selective by analysis of variance. By calculating a binned estimate of behavioral performance (% correct) and correlating this value with the firing rate of neurons, a subpopulation of visually responsive neurons showed enhanced correlations as a function of changes in the behavior (i.e., changing cells). From this subpopulation, authors identified two distinct types of neurons that were correlated with changes in the behavior, either by increasing or decreasing their response to the stimulus or delay period. The time course of the shift in neural responses in relation to behavior was extremely varied, either leading or trailing the actual learning curve. This variation in neurobehavioral relationships was suggested to be indicative of the gradual recruitment of hippocampal neurons into "ensembles" encoding the associations, though a more conclusive test of this hypothesis does not yet

exist. Moreover, it has been shown that hippocampal neurons can be sensitive to body motion (O'Mara et al., 1994), there is a possibility that the observed responses may be related to motor or preparatory-motor responses.

One unanswered question in primate neurophysiology is how groups of hippocampal neurons organize their activity. Theoretical proposals (Jensen and Lisman, 2005; Maurer et al., 2006a) and experimental data in rodents (Skaggs et al., 1996; Montgomery and Buzsáki, 2007; Colgin et al., 2009b) have suggested that neural ensembles may be organized by oscillations in the local field potential—though evidence for such a role in the primate hippocampus is relatively spare. One study has found an enhancement of gamma band (30-100Hz) activity during memory encoding in the hippocampus (Jutras et al., 2009). There was a significant increase in the coherence between gamma activity and the spiking activity of single neurons during this period, and the magnitude of coherence was predictive of subsequent recall performance (Jutras et al., 2009; but see chapter 5 for further discussion and criticism).

One puzzling feature of many published reports is the dramatic differences in baseline firing rate properties when compared to the rodent literature (See table 2.1). Many papers fail to record the waveforms of individual spikes, which preclude the ability to make statements regarding neural type. Moreover, several neurons that show high firing rates (> 15 Hz) are dubbed putative interneurons even when these neurons show clear visual selectivity, which is generally not a feature of interneurons. These types of high firing rate neurons are often indicative of regions such as the perirhinal

cortex (which is located directly below the hippocampal formation). In addition, while interneurons in the rodent have been shown to modulate their firing rate based on novelty, the change is generally measured as an enhanced baseline firing rate, not a change in visual selectivity (Nitz and McNaughton, 2004; Karlsson and Frank, 2008). Finally, a number of these studies do not include histological reconstructions with which to identify the electrode path. When tract reconstruction is paired with waveform and spiking characteristics of individual neurons, physiological data are much more in line with findings published in the rodent literature suggesting that hippocampal activity is much more sparse than that observed in cortical regions upstream of the hippocampus (Rolls, 1999; Hori et al., 2005; Skaggs et al., 2007). Taken as a whole these observations suggest that data in a number of published findings reporting the activity of hippocampal neurons may not be hippocampal in origin.

Laboratory	Species	Histology	Task	# Cells	Firing Rates (baseline)
Barnes					
Skaggs 2007	M.M	Y	Mnemonic	618*	< 1Hz
Buffalo					
Jutras 2009	M.M.	No	Mnemonic	88/131	7 Hz
Brown					
Xiang and Brown 1998	M.M.	Y (partial)	Mnemonic	40/283	n.r
Fried					
Fried 1997	H.S.	N	Mnemonic	29/33	n.r
Ekstrom 2003	H.S.	N	Spatial	67	n.r
Quiroga 2005	H.S.	N	Mnemonic	27/60	n.r
Gelbard-Sagiv 2008	H.S.	N	Mnemonic	89/184	n.r

Ludvig					
Ludvig 2004	S.S.	Y	Spatial	8/28	< 1 Hz
Ono					
Hori 2011	M.M	N	Spatial	83	< 1.5 Hz
Eifuku	M.M	N	Spatial	88/329	< 1 Hz
Matsumara 1999	M.M	N	Spatial	166/389	< 1 Hz
Nishijo 1997	M.M	N	Spatial	156/238	< 2 Hz
Ono 1991	M.M	N	Spatial	77/174	n.r
Hori 2005	M.M	N	Spatial	72/228	< 2 Hz
Rolls					
O'Mara 1994	M.M	CT Scan	Spatial	46/461	12 Hz
Georges-Francois	M.M	CT Scan	Spatial	40/354	< 1 Hz
Rolls 1999	M.M	Y/CT	Mnemonic	15/660	n.r
Suzuki					
Yanike 2004	M.M.	MR Only	Mnemonic	**	**
Wirth 2003	M.M.	MR Only	Mnemonic	89/145	8 - 45 Hz
Wirth 2009	M.M.	MR Only	Mnemonic	83/127	n.r
Naya 2011	M.M.	MR Only	Temporal	53/193	n.r
Yanikie 2009	M.M.	MR Only	Mnemonic	65/85	24.21 Hz

Table 2.1 - Rates of hippocampal neurons recorded across a laboratories
Acute hippocampal recordings are the norm in primate neurophysiology owing to a variety of factors. Critically, a number of studies have reported baseline firing rates of neurons which were considerably higher than what is known from hippocampal units in rodents and studies with primates for which histology is available. Moreover, this meta analysis revealed a disturbing trend for researchers to not report raw firing rate measures, or waveforms of the units recorded. Species key: H.S- Homo Sapien, M.M - Macaca mulatta, S.S -Simia sciureus. * No differential behavioral activity reported. Cell numbers (task responsive neurons)/total neurons recorded. n.r - did not report firing rate summaries, only individual examples given.

Disregarding the potential flaws in data acquisition and whether data are collected from the intended recording site, the evidence suggesting that the hippocampus plays a role in encoding visual stimuli or in mnemonic processes is ambiguous. To begin, while there are apparent differences in the responses of single

units, it is not clear whether these responses are actually a result of an intrinsic computation of the hippocampus or whether these neurons simply reflect the changes in responses of neurons upstream to the hippocampus which have been demonstrated to show the identical changes in responses to novelty (e.g., Miller et al., 1991; Sobotka and Ringo, 1996; Xiang and Brown, 1998). The interpretation of these data is further complicated by the conspicuous absence of high quality anatomical electrode localization. Moreover, there have been no studies to date conclusively demonstrating that the responses of hippocampal neurons are necessary or sufficient to mediate recognition memory, or whether these changes simply reflect changes in the activity of neurons upstream. However, it should be noted that some of the mnemonic findings from single-unit recording studies are in line with results from functional imaging studies in humans which show similar sensitivity of the hippocampus the relative familiarity of an object (e.g., Strange et al., 1999; Daselaar et al., 2006; Kumaran and Maguire, 2007).

2.3.5 Spatial Properties of hippocampal neurons

First described in rodents, the activity pyramidal neurons in the CA fields and granule cells in the dentate gyrus are significantly modulated by an animal's position in space, earning them the name "place cells" (O'Keefe and Dostrovsky, 1971; Jung and McNaughton, 1993). Multiple single-unit recordings indicate that for any environment approximately 40% of CA1 neurons show this place specific firing. When the place activity of many neurons is combined, the activity of the population of neurons covers

the entire environment and can be used experimentally to reconstruct an animal's path through an environment (Wilson and McNaughton, 1993a; Zhang et al., 1998). Importantly, this activity is diminished if self-motion cues are removed (e.g., if the environment is traversed by "driving a car") or abolished if animals are completely restrained (Foster et al., 1989; Terrazas et al., 2005). In addition, spatial selectivity of these neurons persists in the dark and is sensitive to changes in local and distal cues as well as changing behavioral demands (Markus et al., 1994; Knierim et al., 1995, 1998; Gothard et al., 2001).

Several studies of the activity of putative pyramidal neurons from the hippocampus of behaving primates have demonstrated a variety of place-selective activity that can be grouped into three major types. Several studies in which primates were placed in a primate restraint chair and allowed to move themselves around a square arena have demonstrated that approximately the same proportion (~40%) of these neurons show place selective firing with some apparent similarities to those found in the rodents (Ono et al., 1991, 1993; Matsumura et al., 1999; Hori et al., 2003, 2005). As in rodents, the activity of these neurons can be used to reconstruct an animal's path through an environment and the accuracy of this reconstruction is reduced when animals must use a pointer to recreate the path on a screen (Hori et al., 2003). Interestingly, one study found that approximately 13% of hippocampal neurons jointly signaled a combination of place and task/environment related information (Ono et al.,

1993). It is possible that this conjunctive coding serves as the neural substrate for episodic memory.

A second type of responses of hippocampal pyramidal neurons, first described by Rolls and colleagues, are responsive to an animal's view of the environment. These neurons can respond either to a particular portion of the visual environment (e.g., the top right corner of the room, independent of animal position), while others are sensitive to view but only from a particular location in space (e.g., selective to the top right corner, but only when facing it from the left corner of the room) (Robertson et al., 1998; Rolls, 1999; Rolls et al., 2005). It has been proposed that the activity of these neurons represents the presence of both egocentic and allocentric-based spatial information in the primate hippocampal formation. Interestingly, it appears that CA1 neurons maintained their firing preference when a previously unobscured environment was hidden by a curtain, but CA3 neurons stopped responding (Robertson et al., 1998), demonstrating the importance of visual details for CA3 neurons. It should be noted that the observed differences in responding could be due to rate remapping (i.e., retention of spatial selectivity but with a significant modulation in firing rate), as has been shown to occur in rodent CA3 neurons when changes are made to the environment (Muller and Kubie, 1987; Leutgeb et al., 2005, 2007). Lastly, a group of neurons showed correlated firing in relation to specific types of body motion (O'Mara et al. 1994, Rolls & O'Mara 1995). Single unit activity recorded from the hippocampus and parahippocampal region of neurosurgical patients while subjects navigated a virtual town showed both view and

place responses, similar to nonhuman primates and rodents (Ekstrom et al., 2003; Watrous et al., 2011).

2.3.6 The role of the dentate gyrus in hippocampal encoding

In contrast to the activity of neurons in the CA fields, the activity of neurons of the dentate gyrus (DG) is much more sparse (e.g., Jung and McNaughton, 1993; Leutgeb et al., 2007). Unfortunately, virtually no data exist regarding the activity of dentate mossy or granule cells in behaving primates, thus necessitating a brief review of the rodent literature. However, it should be noted that there are significant differences in the cytoarchitecture of dentate region between rodents and primates (see section 2.1.6 for review). Molecular imaging studies of activity dependent gene expression suggest that for a given environmental exposure, approximately 2% of dentate neurons are active (Chawla et al., 2005; Ramírez-Amaya et al., 2005; Alme et al., 2010), underscoring why reliable electrophysiological recordings are difficult to achieve. The activity of granule cells, similar to that of principal neurons in the CA fields, is significantly modulated by an animal's location in an environment, although the size of their place fields is significantly smaller (Jung and McNaughton, 1993). Among the potential reason for this lower activity is likely to be the more negative resting voltage of dentate granule cells (Barnes and McNaughton, 1980; Spruston and Johnston, 1992; Staley et al., 1992; Penttonen et al., 1997; Spruston and McBain, 2007), meaning that individual granule cells require more synaptic activation before crossing the action potential initiation threshold.

Computational proposals based on the circuit and neuronal response properties of the dentate gyrus have suggested that the ultimate function of the DG may be to pattern-separate incoming entorhinal patterns and create a more pared-down, or sparse, code which can be encoded by neurons in CA3 and CA1. Specifically, the extremely small number of granule cells are activated by a given experience (or episode) results in the activation of a sparse and non-overlapping population in CA3.

Working in rodents and utilizing a gradually morphing environment that changes from a round to a square arena over several steps, Leutgeb et al., (2007) were able to demonstrate that while CA3 neurons gradually altered their activity to track the changes in an environment, dentate granule cells showed highly dissimilar patterns of spatial selectivity to even minor changes in the environment, though the same population of dentate granules remain active throughout. At the population level, this dissimilar activity implies a unique pattern of neural activation for each environment, a central prediction of the orthogonalization/pattern-separation theory of dentate gyrus function (Marr, 1971). In addition, several studies have shown patterns of activity in the human dentate gyrus compatible with the pattern separation hypothesis (e.g., Bakker et al., 2008; Lacy et al., 2011), with additional evidence pointing towards impaired pattern separation abilities and that these deficits may be associated with dentate dysfunction (see Small et al. 2011 for further discussion).

Single-unit (Leutgeb et al., 2007) and molecular imaging studies (Alme et al., 2010) have demonstrated that the same population of dentate neurons is active across

different environments, which makes it difficult to understand how this pattern of activity could actively orthogonalize different input patterns. Alme et.al (2010) demonstrated that the majority of granule cells are active in a given an environment (i.e., show place selective firing or are labeled positively for molecular markers specific to increases in activity) likely belong to a population of newly generated (i.e., adult born) granule cells. The authors further demonstrated that granule cells eventually "retire" and no longer respond to experiences/environments, calling into question how a group of "retired" granule neurons could participate in the retrieval of memories in CA3. Consequently, the high percentage of overlap between different environments along with the selective "retirement" of older granule cells, provides a significant challenge to the orthogonalization theory of dentate function. However, the recruitment of a new population of granule cells, which would theoretically lead to the recruitment of a new population of CA3 neurons, is a central feature of the multiple trace theory.

2.3.7 Summary Hippocampal Physiology

Clinical, behavioral, and electrophysiological data support the notion that the hippocampus can serve as a mnemonic, spatial, and possibly perceptual structure; a notion underscored by deficits produced by lesions to the structure. Mechanistically, these functions are embodied by the hippocampus' ability to rapidly form associations between a wide variety of cortical inputs, and to act as a high-level pattern separator which can encode cortical information in a sparse and highly abstracted neural code.

The construction of associations between the spatial context and features of the environment (e.g., people and objects) forms the foundation of episodic memory. However, physiological data supporting these theories—especially in humans and primates—is not available. Future studies must:

1) Examine the prediction that hippocampal associations can serve as an *inde*x through which exposure to a subcomponent of an experience (e.g., an odor) is able to reinstate the experience in its entirety.
2) Examine the role of hippocampal back-projections in consolidating memories in the neocortex and whether and how this consolidation process improves the efficiency of encoding at the cortical level.
3) Determine what role of the DG plays in maximizing storage space in hippocampal networks and the precise mechanism by which it transforms cortical codes.

2.3.8 General Conclusion and Summary

The structures of the medial temporal lobe are clearly necessary for the formation of recognition memory. However, a precise delineation of the relative contributions of hippocampal and neocortical (especially inferior temporal) cortex to mnemonic process has remained elusive. At present, the literature suggests that these structures act in concert as a multimodal hierarchal associative network in which the representations of items/events in the environment become increasingly abstract at successive stages within this network. The reciprocal nature of this network further

implies that representations at relatively high levels of abstraction may readily interact—and even modify—lower level representations in more primary cortical areas.

The consequences of this organization are readily apparent, even at the simplest level, when examining the responses of neurons in different subregions to simple visual stimuli. In area TE for instance, a fairly high number of neurons may respond to any given image and one neuron may selectively respond to multiple images. At the level of the hippocampus however, representations are decidedly more sparse, with only a very small percentage of neurons showing any visual responsiveness. This pattern of responding suggests that the two regions use different encoding schemes to represent information. The observed levels of sparsity within the hippocampal network are widely believed to be a consequence of the need to have a large storage capacity in a network which deals with extremely high level abstract representations (e.g., Barnes et al., 1990; Jung and McNaughton, 1993; Treves and Rolls, 1994).

CHAPTER 3- GENERAL METHODS

3.1 Subject history

For the current study, data were recorded from four rhesus macaques, which included: MMU25516 (Buzz) male, 13 years and 6 months at time of euthanasia (birth date 4/30/90, euthanized on 11/14/03); MMU24299 (Clea) female, 18 years and 3.5 months at time of euthanasia (birth date 5/16/88, euthanized on 06/16/06); MMU17298 (Nessim) male, 29 years and 7 months at time of euthanasia (birth date 6/17/77, euthanized on 2/16/07); MMU07119 (Joan), female, 31 years and 8 months old at time of euthanasia (birth date : 8/30/71, euthanasia on 02/16/07). Prior to implantation, all subjects underwent behavioral testing in a Wisconsin General Testing Apparatus (WGTA, Harlow and Bromer, 1938; Harlow, 1959) as part of a cognitive performance evaluation. This evaluation consisted of three tests, including an object discrimination task, a delayed response task, and a delay nonmatch-to-sample test (e.g., Harlow, 1959). Pre- and post-implantation, all subjects participated in multiple neurophysiological and behavioral experiments, details of which can be found in the animal histories, although only the data relating to the VARNOV task are discussed in this dissertation.

3.2 Surgical Procedures

Prior to implantation all subjects received structural 1.5 T MRI scans which were used for surgical planning and scanned in the same magnet for a series of experiments which involved the injection of gadalinium for enhanced contrast for analysis of cerebral

blood volume (Small et al., 2004). Animals underwent four different surgical procedures. For all surgical procedures involving electrode placement, subjects are administered Depakote one day prior, the day of, and the following day to guard against the possibility seizures occurring. During the first surgical procedure small screws are inserted into the subjects skull as well as a headpost and a Crist recording well (Crist Instruments, Damascus, MD) are attached to the subject's skull with dental acrylic. Implantation of the headpost is necessary for the acquisition of eye-movement data via infrared cameras to ensure subjects heads are stable. Infrared eye tracking avoids the invasive procedure of implanting of scleral search coils. The second surgical procedure involves placing a craniotomy at a predetermined location within the Crist recording well over the right hemisphere. Once the craniotomy is complete the hyperdrive (Figure 3.1 A) is placed into the well. The guide cannulae and and tetrodes are slowly lowered (Figure 3.1 B). Once the hyperdrive manipulator is in place, the implant is completely sealed. Sealing the implant significantly reduces the risk of contamination, and hence infection, once the animal leaves the surgical suite.

Following implantation of the hyperdrive, the tetrode recording probes are lowered, cells isolated and each animal underwent several months of neurophysiological testing. Once testing is complete, the subject undergoes a third procedure in which the hyperdrive is removed and the craniotomy is sealed and covered. Once the animal has recovered from the hyperdrive explant from the right hemisphere, it undergoes a final surgery in which the acrylic is drilled away from the

area of the skull in the left hemisphere where the second hyperdrive will be placed. A craniotomy is then made, a Crist recording well is attached with acrylic, and a hyperdrive is inserted. The cannulae and tetrodes are lowered as for the right hemisphere and the animal undergoes another period in which electrophysiological recordings are obtained while the monkey is awake and performing a behavioral task.

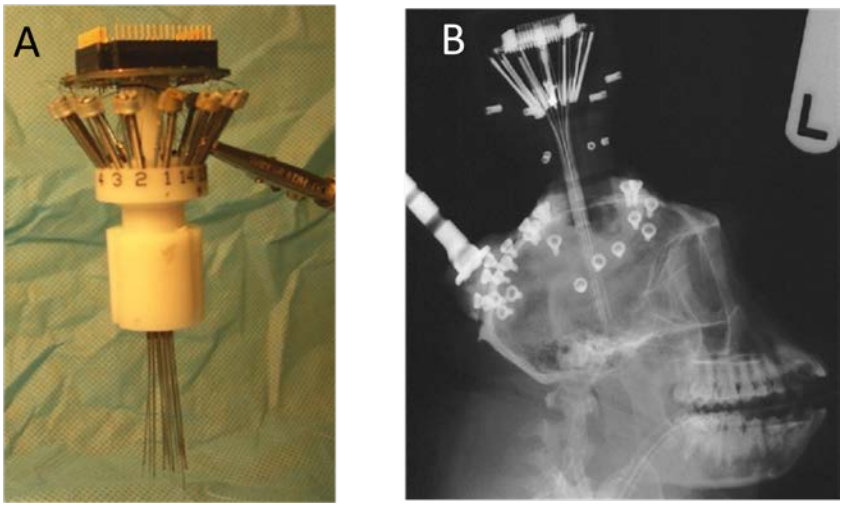


Figure 3.1 - Primate hyperdrive
(A) Examples of hyperdrive with guide cannulae extended. Each cannulae carries one tetrode. **(B)** CT scan of a subject immediately after surgery with guide cannulae fully extended demonstrating the relative position within the brain.

3.3 Primate Hyperdrive

The chronAcsády and Káli, 2007)
ic recording preparation used in the experiment is a derivation and extension of the original hyperdrive for use in rodents (Wilson and McNaughton, 1993b; Skaggs et al., 2007). Each hyperdrive consists of 14 independently moveable tetrodes each of which are contained in and protected by a guide-cannula (Figure 3.1 A). Each guide cannula is attached to a shuttle on a threaded micro-manipulator peg. A 360 degree turn on the peg mounted nut results in an approximate movement of 320 microns of the attached

electrode. The maximum distance for each tetrode varied by animal, but generally around 11-13 mm.

3.4 Necropsy, Histology and Electrode Track Reconstruction

Once data collection from both hemispheres is complete, subjects are retested on the delay nonmatch-to-sample task over the course of several weeks. Once this testing is completed small electrolytic lesions are made approximately 24 hours prior to necropsy. Necropsy procedures begin by administrating subjects with Ketamine via intra muscular injection to produce a level of light anesthesia. Once subject is sedate, intravenous pentobarbital is administered until cessation of the corneal reflex. At this point the thoracic cavity is exposed and the descending aorta is clamped. A small incision is placed in the right atrium and a 20 ga cannula is inserted into the left ventricle up to the ascending aorta. Subjects are transcardially perfused with of 1% parformaldehyde (PFA) in 0.1M phophate buffered saline (ph 7.2) via peristaltic pump at 250ml/min for 2 minutes. The initial perfusion is followed by an 8 minute perfusion with 4% PFA at 250ml/min and continues for an additional 50 minutes but at 100ml/min. During the perfusion process the subjects head is covered in ice.

Once perfusion is complete the head is removed from the body and excess tissue is trimmed from the skull. A bore hole is placed in the foraman magnum and the preparation is submerged in 4% PFA for 12 hours over night allowing tissue around the tetrodes to become more firm. The following morning tetrodes are retracted and guide cannulae are retracted and the hyperdrive removed. Next, the skull is placed in a

stereotax (for stability) and the skull cap and dura are removed. Following dural resection, the anterior and posterior extent of the hyperdrive is marked on the surface of the brain via cuts from a scalpel attached to a manipulator arm, to simplify the post extraction hand cutting of the tissue. The brain is cut into two blocks (front and back) and bathed in 4 % PFA for an additional 6 hours.

Post extraction, tissue is cryoprotected by immersion, for 24 hours, in a 20% glycerol solution at 4˚C + 2% DMSO (Dimethylsulfoxide). Following the initial immersion the solution is increased to 20% glycerol and bathed for a further 72 hours. Following this process, individual blocks are immersed in isopentane which has been chilled in a dry ice / ethanol bath. Freezing time varies from 20 - 40 minutes depending on the size of the blocks. Blocks can then be stored at -72˚C indefinitely, but 24 hours at a minimum, before sectioning.

Blocks of tissue are sectioned coronally at 30 µm on a sliding microtome. Sections are assigned to one of four series (Series 1 contains section 1,5,10, etc, Section 2: 2,6,11, etc ...). Of these, one series is stored in formalin for a minimum of 2 weeks before being processed for Nissl stains. These Nissl sections provide a complete atlas of each animal's brain. Another series is stained with Flurojade throughout the extent of the electrode trajectories for identification of the tips of the tetrodes to help with electrode track reconstruction (Schmued et al., 1997). The remaining two series are stored at -20˚C in tissue cryoprotectant consisting of TCS solution of 30% ethlylene

glycol and 20% glycerol in a sodium phosphate buffer (ph 7.4). Nissl stained slides are imaged at high resolution to reconstruct electrode tracks (Figure 3.2 B).

Post-surgical CT scans are used to visualize individual cannula trajectories (Figure 3.2 A). During the recording sessions a daily log of the distance traveled by an individual electrode is maintained. With these data, in conjunction with plots that give the depth, distance, and neuron number per day (Figure 3.2 C) we are able to reconstruct the approximate location of a tetrode on a given day. Reconstruction data are further verified by examining the baseline firing rates and waveforms of individual neurons (e.g: as in (e.g., Bartho et al., 2004; Skaggs et al., 2007)), as well as hallmarks of the local field potentials such as K-complexes and sharp waves (e.g., Skaggs et al., 2007; Johnson et al., 2010)

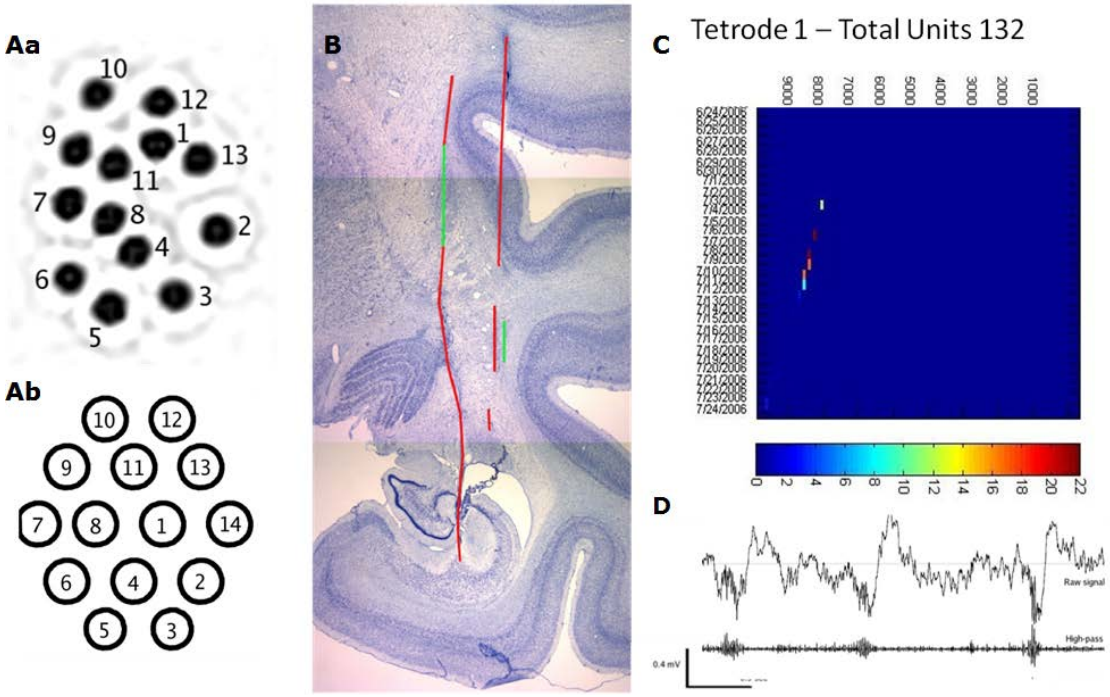


Figure 3.2 - Example of reconstruction/electrode localization technique

Combination of procedures used to localize electrode position. **(Aa/Ab)** Configuration of guide cannulae at the bottom and top of the hyperdrive respectively. Visualizing the relative change in position facilitates determining electrode identity in histological sections. **(B)** Nissl stained section with electrode tracks marked for high (red) or low confidence (green), note the left most electrode (TT1) is easily visualized to its position in CA1. **(C)** Heatmap visualizing **d**ay, depth, and number of neurons (blue 0 neurons - red 22) for TT1. This visualization facilitates visualization of electode position when compared to the figure in (B) and can reveal when an electrode entered/left cell body layers. **(D)** Raw (top) and high pass filtered (bottom) local field potential data. Brain regions show differences in naturally occurring rhythms, for example the hippocampus can show high frequency ripples during quiet wakefulness. These data add an additional layer of confidence to identifying electrode position.

3.5 Neurophysiology - Data Acquisition, Single Unit Isolation, and Analysis

Multiple-single unit and local field potential data are acquired from each tetrode using a Neuralynx Cheetah data acquisition system (www.neuralynx.com). Specifically, single unit data are amplified 2000 times via preamplifiers, and band-pass filtered 600-6000Hz and sampled at 32 KHz. When voltage on one of four tetrode channels exceeds an experimenter set threshold, a 1 ms sample is recorded. Local field potential data is amplified 1000 times and band-pass filtered between 1-475 Hz; these data are digitized at 1 KHz and continuously recorded. Eye movement data are collected in both Neuralynx and a second software package CORTEX (www.cortex.salk.edu) in conjunction with an infrared eye tracking system, ISCAN (Boston, MA). Data are acquired at 120 Hz and broad-cast to both Neuralynx and CORTEX software. In the Neuralynx system these data are treated as a continuously recorded signals similar to the local field potential.

Spike data were further processed offline. Briefly, spikes are sorted according to their amplitude and principal components from the four tetrodes by a clustering algorithm (KlustaKwik and custom C scripts from William E. Skaggs). Data are further

processed using either MClust or custom software (W.E Skaggs). After all processing, clusters of spike trains are assigned a quality and descriptive quality core. This classification produces well isolated single unit clusters and only these units are included in the analyses in subsequent results chapters. Table 3.1 provides an overview of the number of neurons collected over the course of VARNOV for all animals which match this criteria. All analysis routines in the subsequent results chapters were custom written using MATLAB (Mathworks, Cambridge, Ma).

Subject ID	Sessions	Neocortex	Hippocampus	Entorhinal
MMU07119	16	67(4)	0	0
MMU24299	14	0	(2)	6 (1)
MMU17298	17	36(1)	151 (6)	0
MMU25516	45	87(2)	105 (2)	113 (2)

Table 0.1- Unit data
Table cataloging the locations and numbers of neurons recorded from each animal across how many sessions. Number in parentheses indicate from how many electrodes these neurons were recorded. Neuron numbers in this table reflect only well isolated units which were recorded on days during which the animal performed the VARNOV task.

3.6 Behavioral Training - VARNOV

VARNOV (VARiable NOVelty) is a passive viewing task. Specifically, animals are not required to make a behavioral response regarding whether they have previously seen a given stimulus, but are required to keep their eyes directed towards the area of the screen in which stimuli are displayed. The task is controlled via a CORTEX script. For each phase of a trial or behavioral response CORTEX emits an *encode* number assigned to that particular event (e.g., 8- fixation achieved, 35 - image on). These codes are sent to the Neuralynx data acquisition system in a time locked fashion, and provide an accurate time stamp readout of an animal's behavioral state.

Each VARNOV session consists of 50 images which are subdivided into three categories (Stimuli examples in Figure 3.3 A). The first category contains 10 images which were reused every day; these stimuli will be referred to as "familiar" images (RED in Table 3.2). The second category also contains 10 images, but these images were novel at the start of each day. These images are continuously presented throughout the session such that by the end of the day images are familiar. This category is referred to as the "intermediate novelty" category (RED to Green in Table 3.2). The third category contains 30 images which were novel every day (Green in Table 3.2). The images in this category are *refreshed* throughout the session (as described below) to maintain their novelty. VARNOV is run in 3 blocks each consisting of approximately 150 trials. Each trial consists of one presentation each of a novel/intermediate/familiar stimulus, whose intra-trial order is randomized. Novel stimuli are divided into 3 groups of 10 images which are changed to a new group once 150 trials were completed to ensure a high degree of novelty. Novel images are seen approximately 5-10 times.

Block Number	Novel	Intermediate	Familiar	Trials
1	set 1 (novel)	set 4 (novel)	set 5 (familiar)	150
2	set 2 (novel)	set 4 (interm.)	set 5 (familiar)	150
3	set 3 (novel)	set 4 (familiar)	set 5 (familiar)	150

time

Novel → Familiar

Table 3.2 - VARNOV task structure

Table demonstrating the general organization of the task and stimulus sets, as well as the relative novelty of stimuli in the different categories.

The general structure of each trial is as follows. At the start of each trial animals are presented with a fixation spot. Fixation spots are presented until animals have fixated for 250 msec. Following fixation and a brief blank screen, the first image is presented for 2000 msec. After this presentation the screen resets and after a short delay the trial resets with another fixation and starts over with a new image. This structure repeats 3 times (Figure 3.3 B).

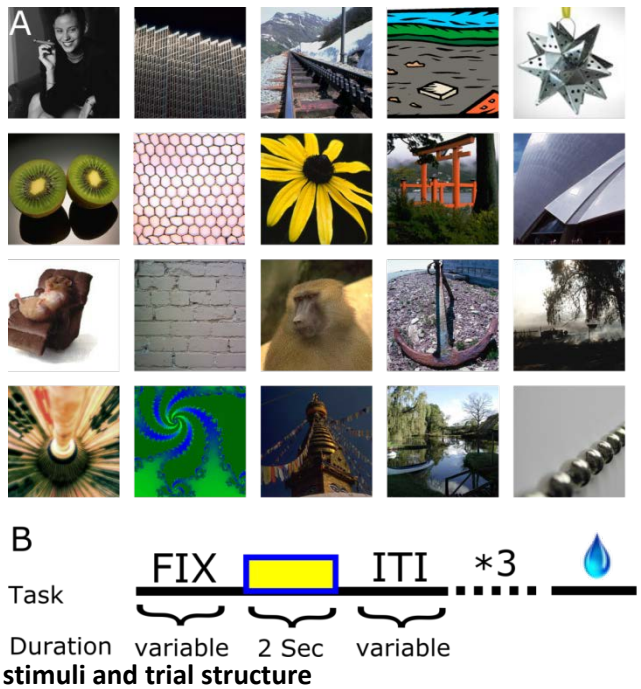


Figure 3.3 - VARNOV stimuli and trial structure
(A) Examples of stimuli used in the task. **(B)** Diagram of one passive viewing trial in VARNOV. Animals are initially presented with a variable fixation delay, after which they are presented with the image for 2 seconds, followed by a variable inter-stimulus interval. In one trial animals are presented with 3 images, one from each of the categories describes in table 3.2.

3.6.1 VARNOV Performance

Previous studies in primates have indicated that primates will preferentially spend more time exploring novel than familiar images (Insel et al., 2008; Jutras and Buffalo, 2010b), although often the time allowed for visual exploration is large (> 5sec). Unfortunately, due to inconsistencies in the performance of the eye-tracking equipment during the time when these data were collected, a rigorous analysis of differences in saccade number or length for these animals is not possible. However, it was possible using session specific adjustments to eye-movement data to arrive at a general estimate of the ratio of time animals spent within the region of the image and time spent outside of the area as a function of the total. Per session, the percentage of time spent looking at the image for all novel and all familiar stimuli was computed, yielding two values. Differences in looking times for each animal were computed by paired t-test; there were no significant differences between novel/familiar looking times for any of the animals (Figure 3.4). The lack of a difference between viewing times for the two conditions likely results from the short (2 second) viewing period. As noted above, differences in looking times for novel/familiar images appear when animals have more time (>5 seconds) to view an image.

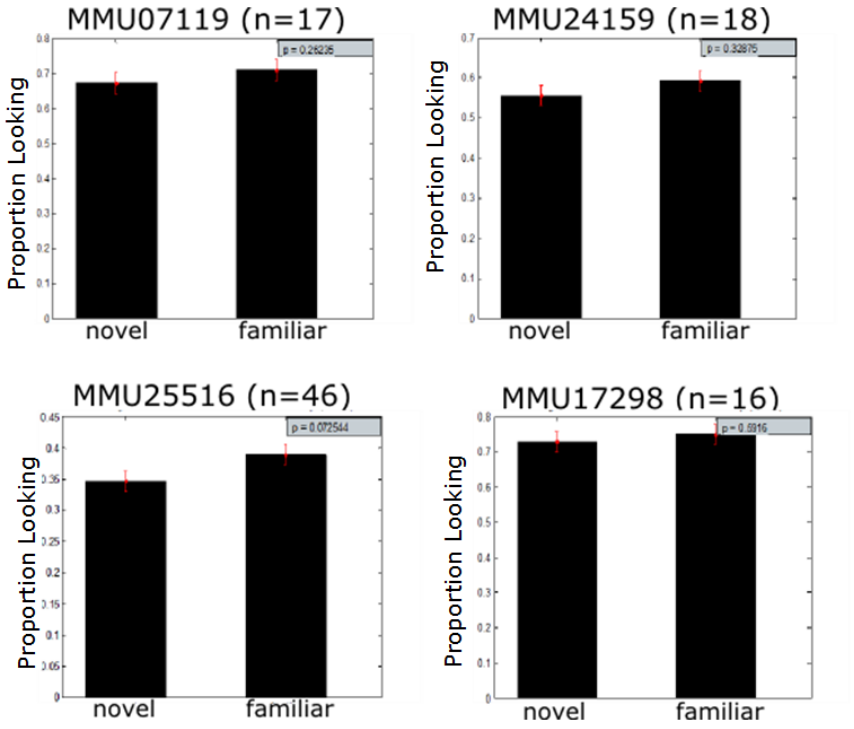


Figure 3.4 - VARNOV Performance
Estimates of the relative proportion of viewing novel vs. familiar computed as the mean for each session for each animal. "n" following animal number indicated number of sessions over which the average was computed.

CHAPTER 4- EFFECT OF EXPERIENCE ON STIMULUS ENCODING IN THE MTL

4.1 Introduction

Information storage in the nervous system can be thought of as discrete populations of neurons representing a particular stimulus or event. In other words, information is encoded in the pattern of active neurons within the population. Critically however, there must exist a balance in the number of neurons representing a particular image in order to maximize the number of unique patterns which can be stored within the circuit. Theoretical proposals have suggested that one mechanism for the brain to maintain encoding efficiency could be by reducing the number of neurons representing a particular stimulus. This reduction in the number of active neurons has two benefits: 1) Increase the number of unique patterns which can be stored and 2) potentially reduce the overlap between two populations of neurons and thereby preventing the misclassification of two stimuli (See Figure 1.1). Tuning of neuronal responses has been observed in multiple regions, including inferior temporal cortex (Freedman et al., 2006). However, virtually all studies describing stimulus tuning in the inferior temporal cortex and medial temporal lobe regions have involved tasks in which animals had to make explicit behavioral responses in order to obtain food/liquid reward. Studies of sensory systems have demonstrated that neural systems can rapidly undergo reorganization (e.g., response tuning) due to explicit behavioral training or even by frequent pairing of certain stimuli with reward. Troublingly, failure to recognize the potential for a behavioral task to exert an effect on an organism's nervous system could lead to faulty

interpretations of the results obtained from an experiment. In other words, the results may not reflect the actual neural mechanisms but rather a physiological adaptation to task demands. Behavioral tasks are often highly simplified and designed, by necessity, to probe an isolated aspect of a complex behavior. Consequently, the task specific adaptations associated with these behaviors may not accurately reflect how the brain solves those more complex behaviors. While this point may seem relatively benign, it is the difference between what the brain *can* do vs. what the brain *does* do.

In light of these facts, the experiments presented below were designed to test stimulus response of neurons in the medial temporal lobe in a more naturalistic setting. The variable novelty (VARNOV) task makes no explicit behavioral demands and does not associate reward with any particular image or image type, allowing us to examine the evolution of neuronal responses in the absence of experimental factors which may shape neuronal responses. Specifically, we tested the hypotheses (outlined in Chapter 1), that in order to maintain encoding efficiency ensembles of neurons in the MTL undergo an experience-dependent tuning. A corollary of this prediction is that if experience induces a change in tuning in individual neurons, then neurons should be more broadly tuned for novel stimuli and more narrowly tuned for familiar stimuli (i.e.: selective for more/fewer stimuli, respectively). Moreover, more narrowly tuned neurons should be better at classifying individual images. To test this hypothesis we implemented an unbiased estimator of neuronal responses.

4.2 Results

4.2.1 Encoding and tuning properties of visually responsive neurons across MTL regions

Neurons were identified as visually responsive if they exceeded the $p < .05$ significance level in a standard t-test comparing the firing rate responses during image presentation vs. fixation firing rate. The percentage, per region, of neurons that showed differential activity in response to visual image presentation is shown in Figure 4.1.

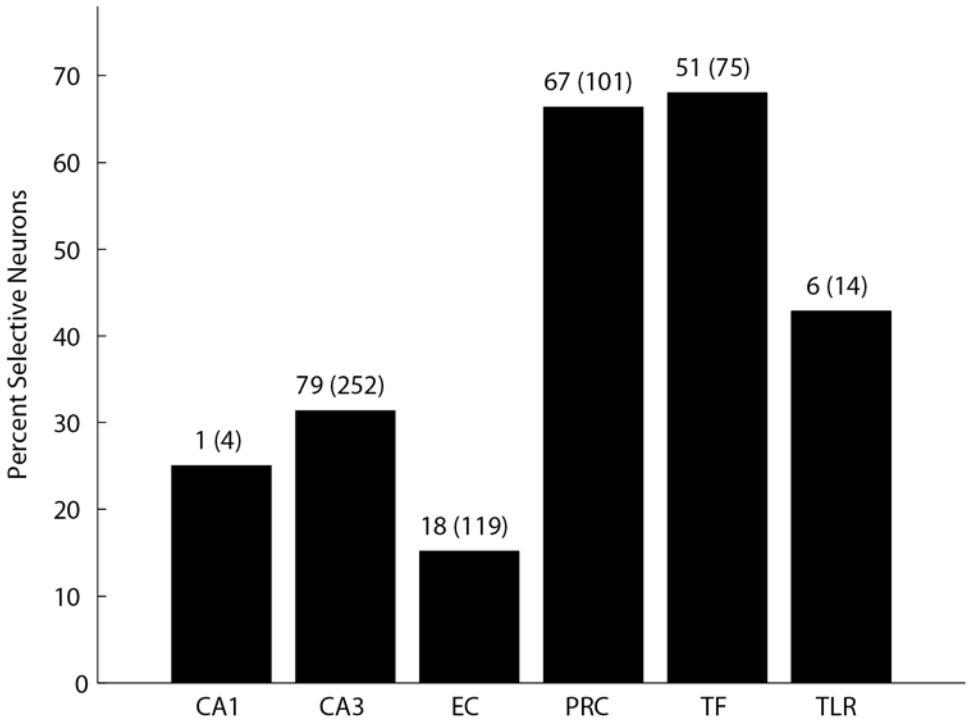


Figure 4.1 - Percent visually responsive neurons per region.
Bar graph showing number of visually responsive neurons (first number) out of the total population of neurons recorded in a given region (in parentheses). Only stable and well isolated neurons are included in these counts. Neuronal selectivity was estimated using one-way ANOVAs (evaluated a $p < .01$).

To further classify whether neurons were *visually selective* (i.e., selective to a subset of presented images), peri-stimulus time histograms (**PSTHs**) were generated for each neuron for each image with 20 ms binning. Representative examples from different MTL regions are shown in Figure 4.2A. For each instance of an image presentation, the visual response of a neuron to that presentation was estimated as the mean firing rate between 75-750ms post stimulus on. A 75ms temporal lag in our firing rate estimation was used to capture the latency with which neurons in the medial temporal lobe respond and to exclude the near 0 firing rate before this onset, which could dilute response magnitude estimates. Firing rates were cataloged in a table n*m matrix for subsequent statistical testing, with one image type assigned to a column with the rows containing the average visual response (in Hz) of the neuron to that particular image presentation. Visually selective neurons were identified by one-way ANOVA ($p < 0.01$) in accordance with previous studies (Erickson and Desimone, 1999; Freedman et al., 2006). To identify images a neuron was visually selective for post-hoc Tukey's HSD against fixation activity were used (Examples in Figure 4.2 B).

The tuning breadth of a neuron can be defined as the percentage of visual images from the total images that a neuron is selective to. Consequently tuning breadth (TB) can defined as $TB = \frac{\#\ selective\ images}{total\_images_{group}}$ x 100. Neurons in area TF and EC showed a significant difference in their tuning breadth, such that neurons were more selective to familiar images than novel images (Wilcoxon two-sample rank sum test, significant P <

0.05, N= 51 and N=18 respectively). Neither CA3 (N=79), PRC (N=67), nor TLR (N=6) neurons showed any changes in their tuning profiles with experience (Figure 4.3A).

To determine whether experience-dependent changes reflect an actual mechanism by which neurons change their tuning profile, we examined the responses of neurons in the intermediate category by estimating the selectivity of neurons to the first four vs. the last four presentations of a stimulus. Neurons in area TF showed an experience-dependent modification in their tuning profile (Wilcoxon two-sample sign rank test, significant $P < 0.05$, N= 51, Figure 4.3B), demonstrating that tuning preferences of a neuron can change within a session.

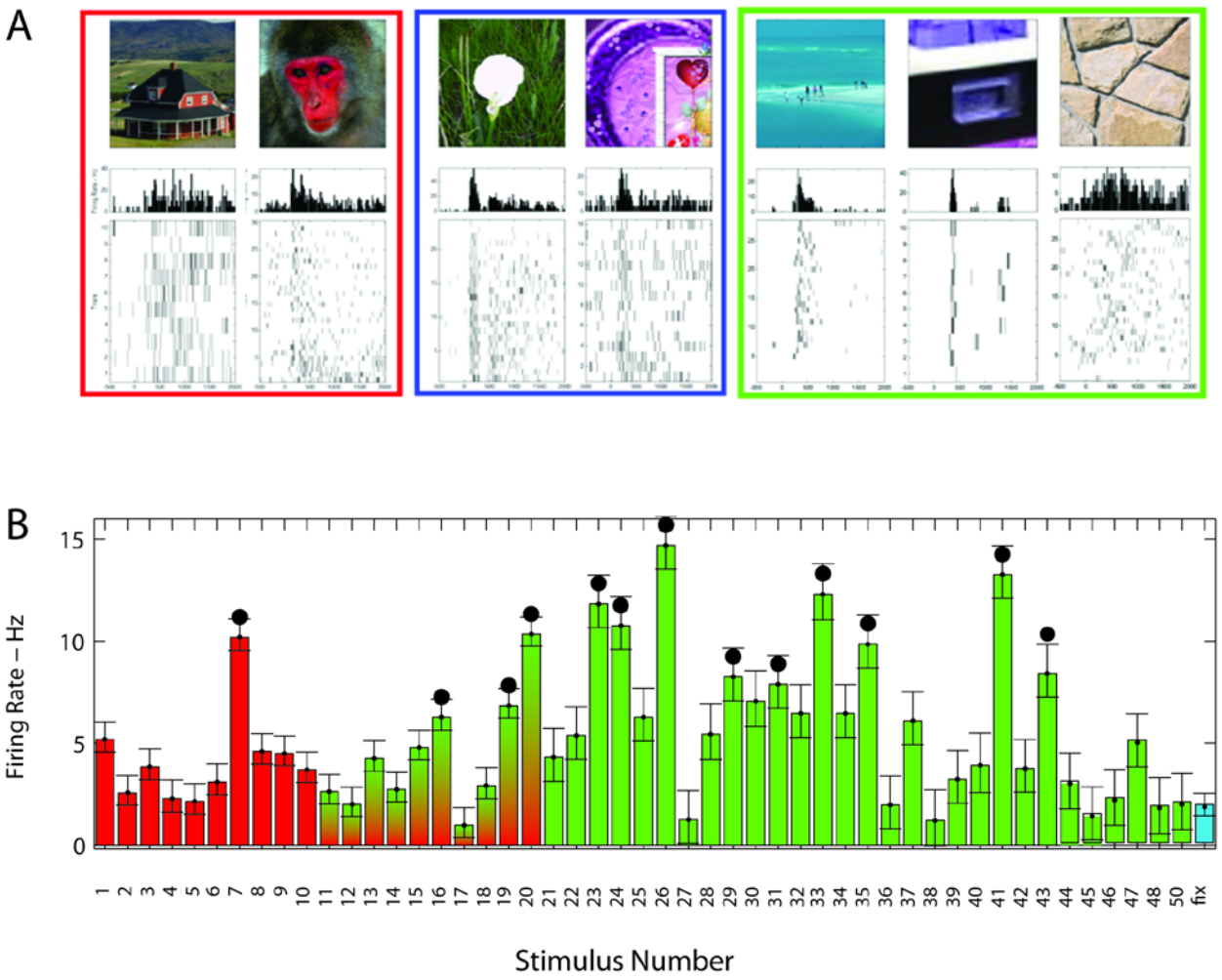


Figure 4.2 - Examples of a visually selective neurons.
(A) Peri Event Time Histograms (PETHs) from individual neurons to one stimulus. Red box – two PRC neurons, Blue Box – two TF neurons, Green box – three CA3 neurons. **(B)** Example tuning profile of a single PRC neuron (10-01_4_1)**.** Firing rate was estimated as the mean response between 75-750 ms. Red bars - familiar stimuli. Green/Red Gradient bars - Intermediate Stimuli. Green bars - novel stimuli. Blue bar - fixation.

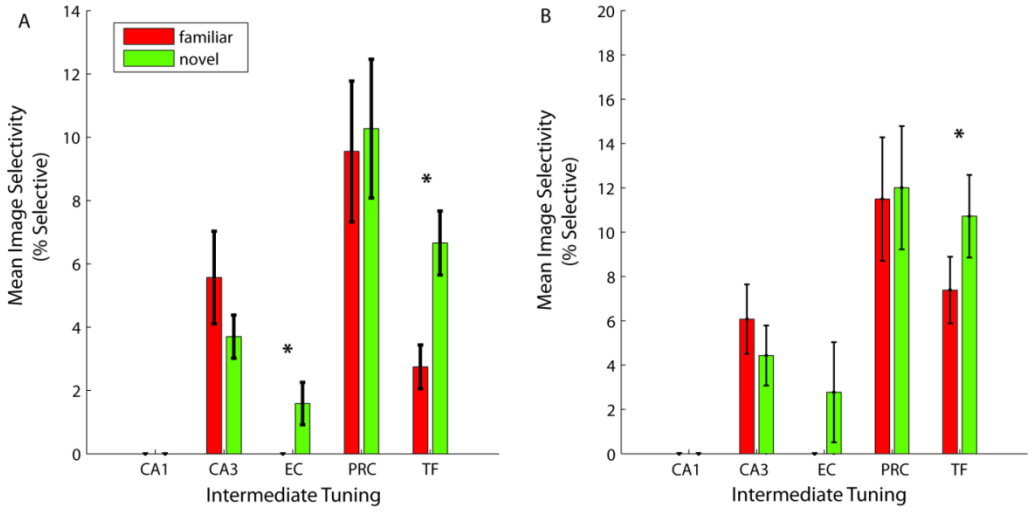


Figure 4.3 - Experience-dependent tuning.
(A) Average selectivity for all neurons within a region in the pure familiar and novel conditions. EC and TF show significant reductions in the average proportion selective for the two categories (Wilcoxon signrank test $p < .05$). **(B)** As in A, but proportion selective is estimated from early and late responses of images in the intermediate category. TF continues to show a significant reduction in proportion tuning difference (Wilcoxon signrank test $p < .05$).

Importantly, while images in the novel and familiar categories are presented equally during the beginning and end of a session, there is no risk of the results being biased due to changes in baseline firing rate. However, given that images in the intermediate category are assessed as the differences in tuning during the first four presentations versus the final four presentations, there exists the possibility that the effects seen in this category are due to changes in baseline firing rate. In order to examine this possibility more closely, baseline firing rates were estimated from the start of the experiment until the last of the first 4 stimuli presentations as well as from the first instance of presentation from the group of final four images to the end of the recorded. A linear regression on the difference score of baseline firing rates ($final\_baseline - start\_baseline$) vs. the difference in the proportion of selective

responses indicated an extremely weak positive correlation ($r^{2=}$0.0269, df =228; p = .0128).

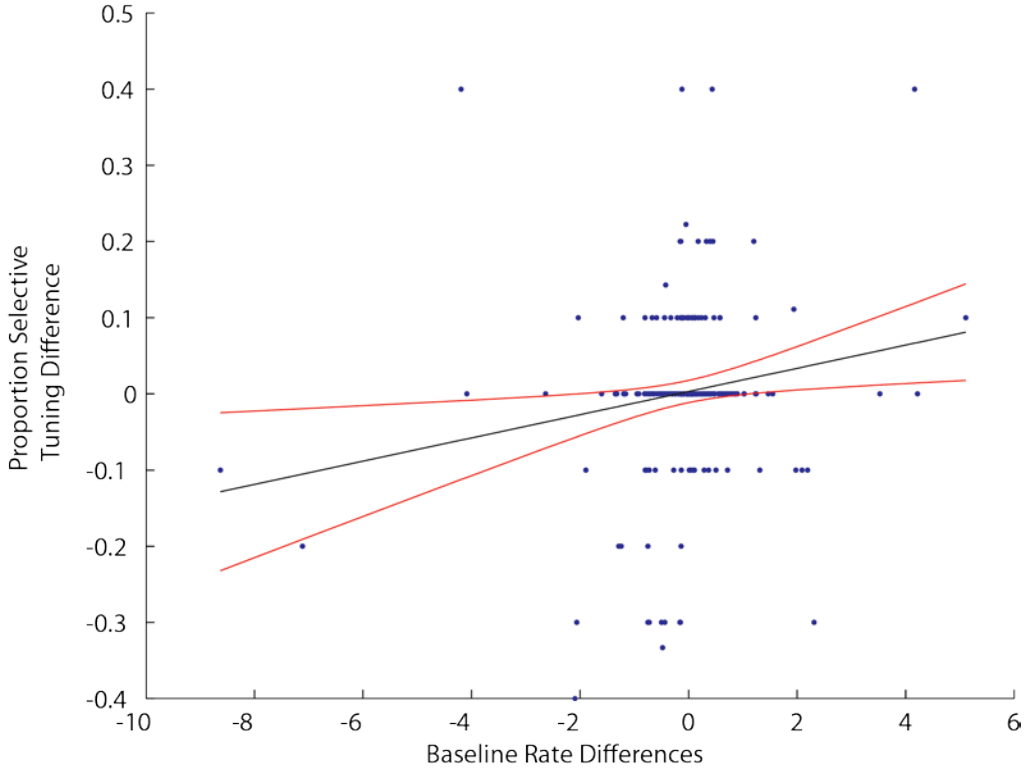


Figure 4.4 - Tuning is not due to changes in baseline firing rate.
Differences of tuning in the intermediate category could possibly be due to changes in baseline firing rate of a neuron in the early and late part of the experiment. Linear regression revealed a very small positive correlation between changes in the tuning response and changes in the baseline rate. Importantly however, the effect appears to be primarily driven by two CA3 neurons with large negativeS rate changes. Red lines represent standard errors of the regression.

4.2.2 Neural responses as classifier inputs for Receiver Operator Characteristic Analysis

The results above indicate that neurons across the medial temporal lobe are sensitive to complex visual images. Specifically, we show that certain images are associated with an elevated neuronal response and we deem these as images to which

the neuron is "selective" (i.e., tuned). Moreover, there appears to exist an experience-dependent tuning in areas TF and EC, such that the neurons respond more selectively to familiar images—suggesting sharper tuning. An additional facet to this observation is whether, an unbiased agent could successfully identify the different images presented to a neuron. Specifically, it may be asked whether narrower tuning corresponds to better classification performance. If so, then an unbiased estimator should perform better for familiar than novel images.

One method for quantifying the performance of a neuron in classifying different images is to estimate its *receiver operating characteristic* (ROC). Britten et al. (1992) were the first to apply this analysis to neural data and correlate the performance of an ROC classifier to the behavioral output of animal. Specifically, they discovered that the performance of an ROC classifier closely matched the psychophysical data. The current analysis implementation is essentially a reproduction of this approach.

Simply stated, ROC analysis compares the rate of true hits (tH) vs. false alarms (fA) for a variety of criterion values. In the context of firing rates, as in Britten et al. (1992), the ratio of tH vs. fA's can be estimated by comparing the responses of a neuron to a particular image to the responses a neuron made in response to fixation, such that tH's now corresponds to the vector of firing rate responses and fA's correspond to fixation related activity. It can then be asked whether, given a particular threshold value of firing rate, an independent observer would correctly classify a given neural response to a particular image or fixation. It is plausible that neurons may be more strongly tuned

to fixation. In this case, these neurons further improve the performance of a classifier as they correctly distinguish the two events. An illustrated example of an ROC analysis is shown in Figure 4.5.

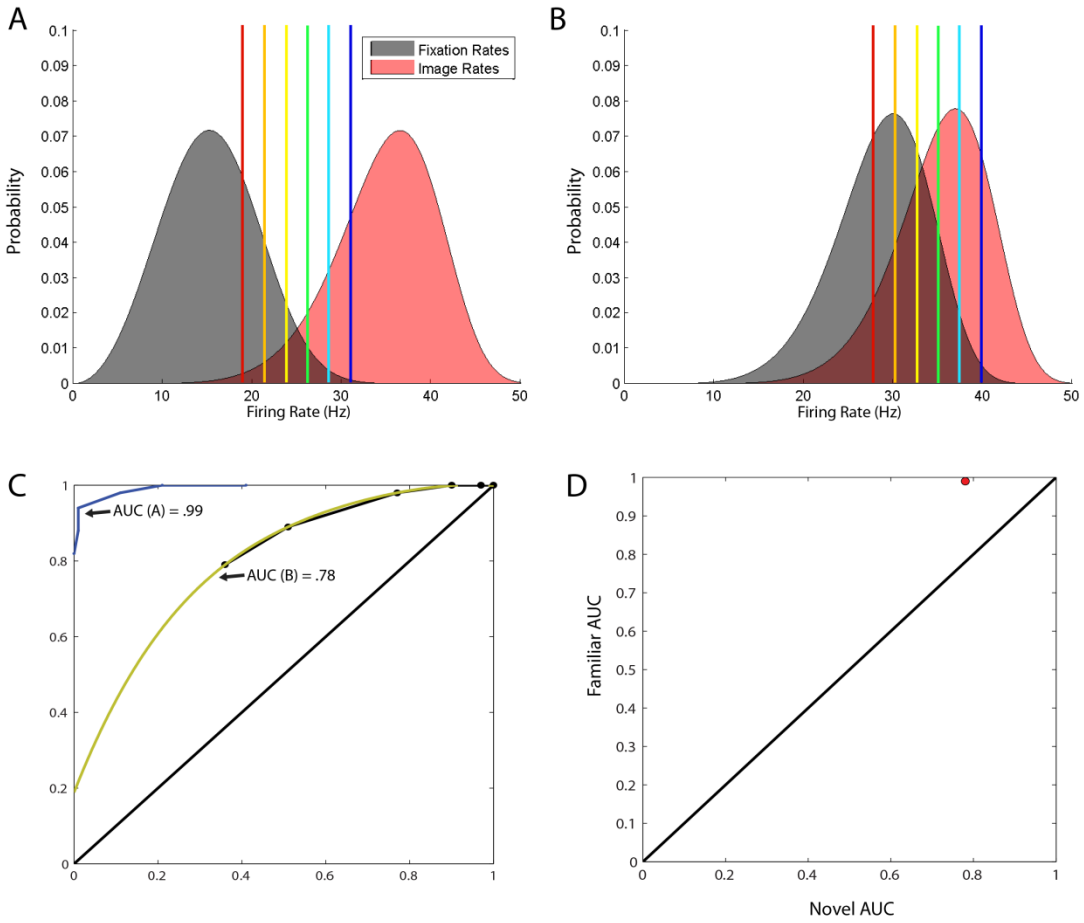


Figure 4.5 - Visual tutorial of receiver operator characteristic (ROC) analysis.
A & B. Simulated firing rate frequency histograms of one "neuron" to a familiar image (**A**) novel image (**B**). Colored lines represent criterion values in firing rates from which the classifying algorithm determines whether a particular response can be reliably associated with an image or not. **C** - Generation of ROC curves by comparing the proportion of Hit vs. false alarms for given threshold values. AUC(A) and AUC(B), refer to the Area under the curve (**AUC**) of ROC curves generated for data contained in figure 4.5 A and B respectively. AUC values are a quantitative measure of discriminator performance, with values of .5 representing chance performance. **D** Hypothetical plot, demonstrating the comparison of two AUC values (from A/B) to determine discriminability of a neuron in response to two conditions. Points above unity reflect enhanced discrimination for familiar stimuli, while points below reflect better performance for novel stimuli.

To estimate the performance of individual neurons in classifying individual images in the novel or familiar category, we computed AUC scores for each neuron for each image. ROC curves were estimated using 40 equally spaced criterion values between 0 and the maximum response of the neuron. The mean AUC of each neuron of images in the novel/familiar category provides an index of how well a neuron performs at classifying individual images. AUC analysis was not performed on neuronal responses to intermediate category images as there are insufficient stimulus presentations (n=4) for novel/familiar respectively. Figure 4.6 shows the comparisons. Notably, neurons that fall within the boundary of the blue square in figure 4.6 perform significantly worse than chance. Poor performance as a classifier can be due to a variety of factors including: a lack of separation between the two distributions, very narrow distributions, or small sample size (stimulus presentations). However, given that we cannot rule out empirical (e.g., no difference between distributions) from experimental factors (e.g., small sample size), these values were not excluded from the present analysis.

Neurons in area TF perform significantly better at classifying familiar images than novel images ($t(32)=-0.38$ $p = 0.03$). However, there was no significant difference between conditions for classifier performance for any other regions ([CA3: $t(18)=-1.5403$ $p = 0.09$], [PRC: $t(30)=-0.53$ $p = 0.42$], [EC, did not t-test, insufficient N]). The results of this analysis match the predictions from the tuning analysis in 4.2.1 that more narrowly tuned neurons should be better at discriminating individual images.

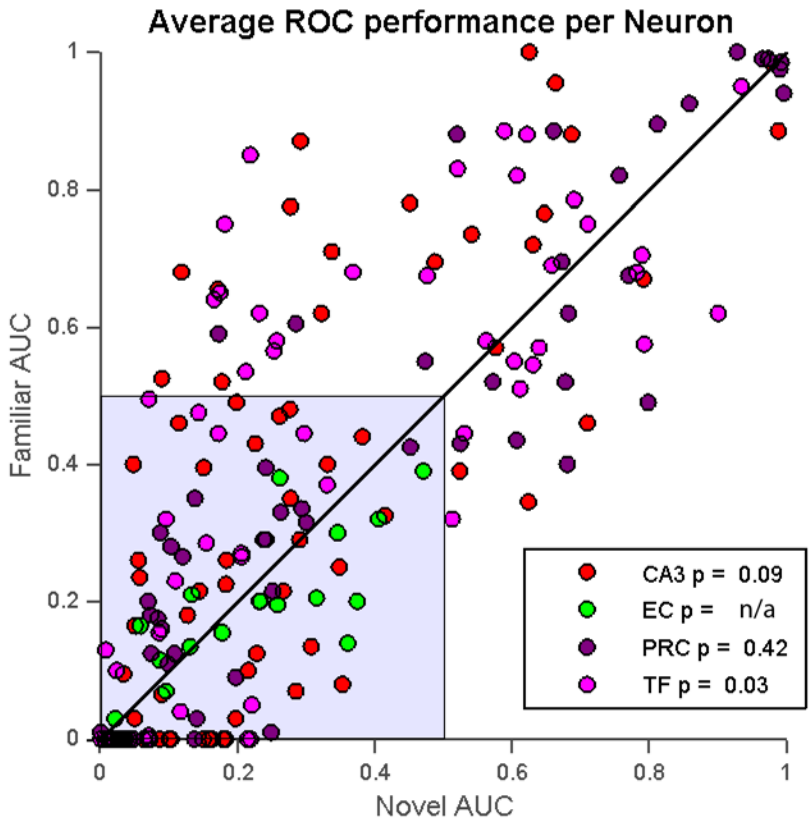


Figure 4.6 - Neuron based reverse discrimination of image identity recapitulates tuning data. As in Figure (4.5 D), comparison of AUC curves for an ROC analysis for novel vs. familiar images. Each point represents the discriminator performance of one neuron. Points above unity reflect enhanced discrimination for familiar stimuli, while points below indicate better performance for novel stimuli. p-values represent result from two-sample t-test. Blue box indicates points which perform worse than chance.

4.2.3 Cell type correlations with visual sensitivity of individual neurons

The macaque medial temporal lobe is composed of a heterogeneous population of neurons, which are characterized by differences in their response properties baseline firing rates. However, it is unclear whether particular types of neurons contribute differently to the encoding process. In the absence of sophisticated anatomical labeling techniques, spiking and waveform characteristics of individual neurons can be used to approximate different cell types (e.g., Bartho et al., 2004; Skaggs et al., 2007; Ison et al.,

2011). Robust predictors of neuron type include: the height of the action potential, the width at half-height, peak area, the depth of the hyperpolarizing valley, width at half depth, and area of the valley (Figure 4.7).

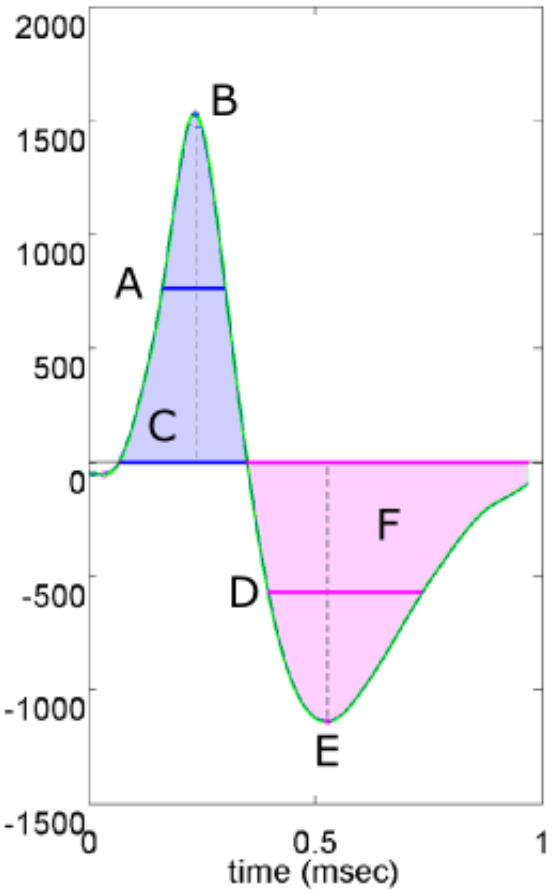


Figure 4.7 - Waveform shape parameters.
Example of the average waveform of a neuron (7-17_5_1) recorded from subject MMU24159 (Winnie). Different parameters of interest are as follow: (A) Width at half-height, (B) peak height, (C) peak area, (D) width at half-depth, (E) valley depth, (F) valley area. Y-AXIS units are normalized A/D units, X-AXIS, milliseconds.

In order to estimate the amount of information about a visual stimulus an individual neuron conveyed in its firing responses ω^2 values were calculated for each

neuron. The ω^2 measure estimates the amount of variance in the neuronal response that can be accounted for by the response of the neuron to different images (e.g., Keppel, 1991; Erickson et al., 2000). ω^2 is given by: $\omega 2 = \frac{\mathrm{SSQcondition - k(-1)MSE}}{\mathrm{SSQtotal + MSE}}$; where SSQ=Sum of Squares & MSE = Mean Squared Error.

Two-dimensional histograms of ω^2 vs. waveform features were constructed, to visualize whether there existed densely clustered regions (Figure 4.8). If a subpopulation of neurons were selectively involved in visual representation, clusters of neurons sharing common features would be expected to emerge. Visual inspection of these plots did not show any significant clustering or trends and no further significance testing was pursued.

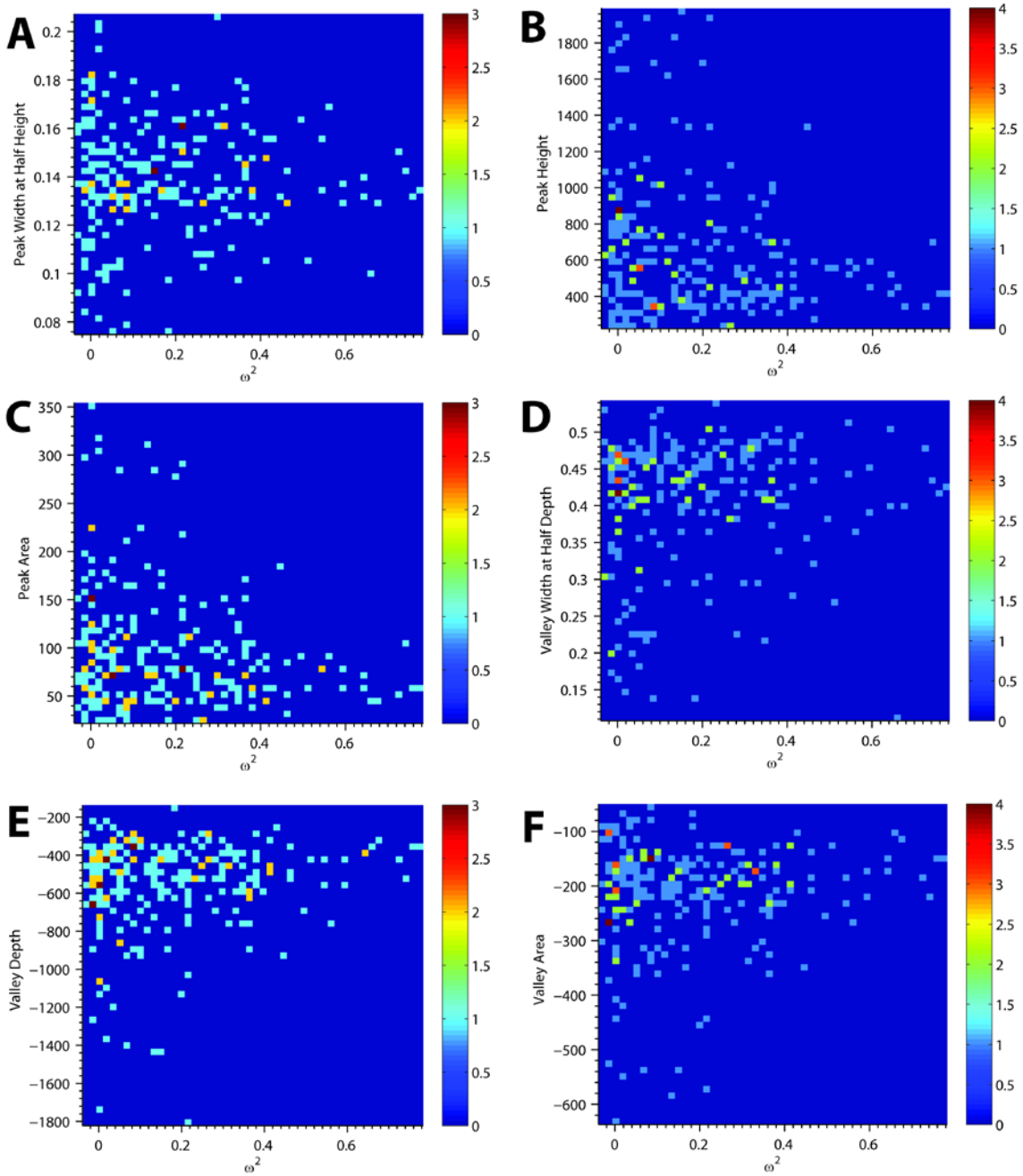


Figure 4.8 - Cell type and ω2 scores.

Attempt to use waveform criteria to identify whether different classes of neurons (i.e., cell types) carried more information about a stimulus than others. (A-F) 2D histograms converted to heat maps (values in red reflect higher densities) of different waveform parameters associated with ω^2 scores. (**A**) Width at half-height, (**B**) peak height, (**C**) peak area, (**D**) width at half-depth, (**E**) valley depth, (**F**) valley area. Heat maps reflect the different relative densities. Suggesting that different cell types do not contribute differentially to information representation.

4.3 Discussion

The series of analyses presented in this chapter indicate a dissociation in the neuronal responses to visual stimuli, with neurons in area TF showing experience-dependent sharpening (i.e., tuning) of their response properties (Figure 4.4). Strikingly, neither CA3 nor PRC show any evidence of experience-dependent tuning. The responses of EC neurons are difficult to interpret, since a comparison between strictly novel and familiar images results in different tuning responses while a comparison between novel and familiar presentations in the intermediate category fails to show a difference. The ambiguity in the EC results may in part be due to the relatively low number of visually responsive neurons recorded (Figure 4.1). The current results are not likely due to the differences in the visual exploratory behavior of our subjects since an analysis of viewing preference (section 3.6.1) indicated no difference in the amount of time spent viewing novel or familiar images.

Experience-dependent tuning has been reported in diverse brain regions from primary somatosensory cortex (Xerri et al., 1999) to TE (Freedman et al., 2006), which our data for region TF strongly support. Notably, our findings of a lack of tuning in the hippocampus do not agree with previous studies in the field. The study by Yanike et al., (2004) recorded single units across the hippocampus (CA3, DG, and Subiculum) of macaques and found evidence for an experience-dependent increase in the selectivity (i.e., sharper tuning) of neurons to familiar images. However, the measure of neuronal selectivity (i.e., tuning) used is independent of whether the neuron was actually

selective to a particular image. The "Selectivity Index" (SI), used in Yanike et al. (2004) is a simple measure, which assesses whether for a given image a neuron has a lower or higher response; if a neuron, on average, responds slightly more to the presentation of one image, but relatively equally to the remaining image, the index will trend towards 1, suggesting an "enhanced" selectivity. However, the mathematical formulation of the SI can easily enhance the responses leading to a magnification of effect size. Moreover, the SI is independent of whether a neuron is statistically selective to a given image. Hence, the SI measure can produce an effect simply by amplifying a very small response by the process of normalization. Further, and in contrast to the measure used in this chapter, it does not take into account statistical variation in the firing rates between repeated presentations of the images. When the data collected for this dissertation is analyzed using the SI measure, neurons from the CA3 region produce a highly significant difference between novel and familiar images ($t(156) = 6.4$, $p < 10^{-8}$). To clarify the relationship between SI values and the measures used in this chapter, a linear regression was performed on these measures for novel trials. This regression suggests that there is no relationship between the two measures (r^2=-0.0026, $t(77) = -0.78$, $p = .4367$, Figure 4.9). The lack of a correlation between these two measures establishes that there is no direct 1:1 relationship between measures such as the SI (based on the construction of normalized ratios) and those measures that are directly based on the number of stimuli a neuron responds to (e.g., Franco et al., 2007; Ison and Quiroga,

2008; Ison et al., 2011). This calls into question the interpretation of Yanike et.al (2004) suggesting that the hippocampus shows experience-dependent tuning.

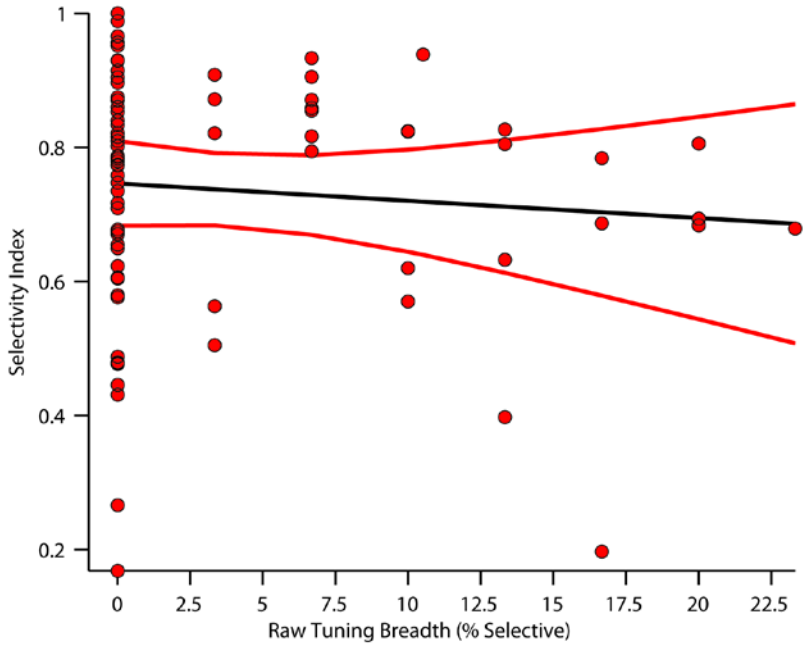


Figure 4.9 - Index does not adequately capture tuning based on firing rate statistics. Linear regression comparing the relationship between the raw tuning breadth as estimated by a Tukey post-hoc test (indicating which specific stimuli a neuron responds to) with the selectivity Index, a dispersion based measure. There is no significant correlation between these two factors, drawing into question the robustness of the selectivity index as a measure of neuronal tuning. Red lines represent standard errors of the regression.

The present data suggest that neurons in inferior temporal cortex (TE) and parahippocampal cortex (TF) regions (as well as more primary sensory areas, see section 2.3.1 for discussion) show an experience-dependent tuning of their response profiles, while neurons of MTL structures (i.e., PRC, hippocampus, possibly entorhinal cortex) do not show a similar tuning response. From an anatomical perspective, a critical distinction between these regions is that parahippocampal and inferior temporal

regions tend to receive significantly more unimodal visual input (as well as visual-spatial inputs from parietal cortex, for example, TF), while the MTL regions tend to receive more highly processed polymodal information (Suzuki and Amaral, 1994c, 2003a). The apparent functional and anatomical dissociation suggests two different mechanisms of information processing and storage between primary-sensory and unimodal cortical areas vs. polymodal association areas.

In cortical regions, specifically those regions involved with processing primary or unimodal sensory information, there may exist a mechanism that actively reduces the number of neurons encoding elemental features of a stimulus. Such a mechanism would ensure a highly specific representation of those elements while also maximizing storage space in the face of having to represent an extremely large set of possible features. In contrast, higher level polymodal association cortices construct a final unified representation of a stimulus, and furthermore act to link multiple stimuli across modalities, in broad agreement with the perceptual-mnemonic theory of perirhinal cortex (e.g. Murray and Bussey, 1999). Hence, the tuning of representations in the PRC (or hippocampus) would be extremely detrimental as they may unwittingly destroy existing associations. Beyond the obvious importance for the construction of "unified representations", it has been suggested that the associational mechanisms of neurons in perirhinal cortex may act to construct view-invariant responses of an object (Miyashita, 1993). Experimentally, this view is supported by recordings from primates (Booth and Rolls, 1998) and imaging studies in humans (Devlin and Price, 2007).

Finally, it should be noted that enhanced specificity (i.e., more narrowly tuned neuronal responses) does not necessarily result in an enhanced storage capacity. Specifically Zhang and Sejnowski (1999) demonstrated that as the dimensions of a stimulus or an environment increase (e.g. multiple visual features simultaneously present in an environment), representations supported by a population of narrowly tuned neurons can become unstable. In the model of Zhang and Sejnowski (1999) this instability does not occur when the supporting population of neurons is more broadly tuned. This prediction however is not necessarily supported by experimental data. Specifically, it has been demonstrated that when objects are embedded in a natural scene, the receptive fields of neurons in IT cortex become smaller, without changing their tuning breadth (Sheinberg and Logothetis, 2001; Rolls et al., 2003). Moreover, it must be noted that the representation at the neuronal level can vary depending on whether a stimulus is presented foveally or at a parafoveal location (Aggelopoulos and Rolls, 2005). Consequently, while interesting from a theoretical perspective the mechanism proposed by Zhang and Sejnowski (1999) likely requires revision to account for the intricacies of the organization of the nervous system.

A final possibility regarding the nature of the experience-dependent changes observed in the current body of work is that they may be linked to the development of a gist-like representation of a stimulus. Gist may be broadly understood as the essence of an item (e.g., it's *chairness*). Because the stimuli used in the present experiment would be difficult for animals to group into broad categories the current data are unlikely

related to the formation of gist. However, it is possible that, the development of gist is related to the development of categorical representations. Studies in the inferior temporal (IT) cortex of behaving rhesus macaques have indicated that when animals undergo lengthy instruction in category discrimination (e.g., cat vs. dogs), the responses of IT neurons shows a similar experience-dependent increase in their specificity.

As discussed in Chapter 2, data collected from rodents and primates have suggested that the decrementing or incrementing activity of neurons in perirhinal cortex and hippocampus may be mechanistically related to the relative novelty or familiarity of a stimulus. The current data, however, do not generally support this view for several reasons: First, in the data collected for this dissertation no neurons respond exclusively to either novel or familiar images, as would be predicted if the neurons were encoding either novelty/familiarity. However, it may be argued that neurons encode the relative familiarity or novelty of a stimulus via small changes in firing rates without significant changes to their stimulus selectivity. This possibility can be addressed via two related measures. One, it can be asked whether single neurons respond to novelty by decreasing its firing rate between the first and second stimulus, or two, whether it's firing rate is sensitive to relative familiarity of a stimulus by increasing its rate between the second and third stimulus. The second reason is that, it may be asked whether there is a difference in the mean firing rate response to the first few instances of an image presentation vs. the last few presentations for all images. If neurons are truly novelty/familiarity detectors, it would be expected that they should show the responses

of the type described above for a vast majority of stimuli. Only novel images were used for this analysis, as responses to these images would be expected to show the full spectrum of familiarity/novelty responses. To allow for some background variation, it was only required that the neuron showed a differential response to 75% of images, 100% criterion was not used as it may be too stringent. Strikingly, no neurons in any region were exclusively (> 80% of responses) sensitive to either familiarity or novelty of a stimulus. Theoretically, the threshold could be lowered, but it becomes difficult to understand how neurons receiving a recognition memory signal (i.e., novel/familiar) could discriminate the message when the signaling neuron is sensitive to changes in both conditions. Moreover, differences in rates were often quite small, on the order of a few spikes, which in the face of unreliable synaptic transmission (e.g., Allen and Stevens, 1994) in the medial temporal lobe further puts into question how such minor differences could be computationally meaningful.

Three factors may account for the striking differences between our study and previous studies in terms of novelty and familiarity discrimination. First, the discrepancy between ours and previously reported data is that the authors of those studies, by virtue of their recording methodology, unwittingly preselected the neurons they recorded from, thereby biasing their estimates of their prevalence in the population (see also section 2.3.1, for a discussion of the shortcomings of the interpretation of response decrement theories). Secondly, several reports which suggest the existence of explicit novelty signals, employ mathematical analyses similar to those of Yanike et.al

(2004). These methods are extremely sensitive to very small fluctuations in firing rate and do not control for intrinsic neuronal variability. Importantly, if these analyses are measuring only small/weak fluctuations in rate, the critical question becomes how the brain manages to decode such small signals when they generally fail to rise above the statistical background noise of the neuron.

Third, many (e.g., Xiang and Brown, 1998; Hölscher et al., 2003; Freedman et al., 2006), but not all (Jutras and Buffalo, 2010), of the previous studies used tasks which require subjects to make explicit behavioral responses indicating whether a stimulus was novel or familiar. Overt responses and overtraining has been shown to lead to dramatic rearrangement of neuronal responses across several cortical areas (e.g., Bao et al., 2003; Zhou and Merzenich, 2007; Guic et al., 2008). Given that animals receive significant amounts of training prior to recording, it may be possible that novelty/familiarity responses are not an intrinsic feature, but rather represent a training related adaptation. For example, neurons in the PRC can show rapid training related adaptation when animals have to learn a new task (e.g., PRC neurons will show pair-coding activity in some cases within 40 trials, Cynthia Erickson personal communication). Moreover, the pairing of behavioral responses with reward delivery is a complicating factor as reward delivery can elicit robust increases in the activity of dopaminergic neurons in the ventral tegmental area (e.g. Ljungberg et al., 1992). Dopaminergic afferents project throughout the MTL and the presence of dopamine significantly enhances LTP induction and consequently learning (e.g., Otmakhova and

Lisman, 1996; Wittmann et al., 2005; Lisman and Grace, 2005), further putting into question the existence of true novelty responses.

CHAPTER 5- EXPERIENCE-DEPENDENT CHANGES IN TEMPORAL CORRELATIONS BETWEEN NEURONS

5.1 Introduction

The organization of information processing in the nervous system is characterized not only by the responses of individual neurons to different stimuli, but is further defined by the activity between neurons. This view of information processing is perhaps most succinctly captured by the paraphrase of Donald Hebb's idea that: *neurons that fire together, wire together* (Schatz, 1992); with an emphasis on together. However, this view of perpetual strengthening of connections between neurons is not without fault. Specifically, if learning in the nervous system develops via the enhancement of connections between neurons, what are the factors preventing the saturation of the nervous system by this strengthening? Selective weakening of extant connections between neurons may be an efficient mechanism by which the brain a) can prevent network saturation and b) enhance differences in network activity between highly similar/competing states (i.e. preventing interference; Figure 1.3). The physiological candidate mechanism serving such a weakening of connections is long term depression (LTD). Multiple lines of evidence from combined electrophysiological and retrograde tracing experiments in primates to *in vivo* and *in vitro* viral manipulations in rodents have begun to demonstrate a critical role for LTD in the recognition memory process.

A fundamental question for neuroscience is to understand how behavior and the environment shape the structure of cortical networks *in vivo*. However, tracking the changes in network structure *in vivo* remains a fundamental challenge for the field. An alternative approach to understanding the dynamic connectivity of neural networks *in vivo* leverages the statistical relationships between neurons to discover signatures of functional connectivity between them (e.g., Griffith and Horn, 1963; Toyama et al., 1981; Aertsen et al., 1989; Thomson and Lamy, 2007). Section 5.2.1 and 5.2.2 will offer an introduction to correlation analyses and describe the more sophisticated analytical methods used in the current dissertation. Section 5.3 describes the results of our analyses testing the hypotheses that networks may undergo an experience-dependent change in the strength of their temporal correlations. Finally section 5.4 summarizes and draws conclusions for the presented findings.

5.2 General Methods Quantifying Neuronal Correlations

5.2.1 Brief introduction to measuring temporal correlations between pairs of neurons

The principle assumption for any correlation measure is that if a neuron A has an excitatory projection to neuron B, such that A reliably participates in firing of B (analogous to Hebb's theorem), then statistically there should exist a positive correlation (or negative in the case of inhibition) between the two. The standard method of comparing these differences is known as the crosscorrelogram (**CCG**).

When computing the CCG between two neurons, one neuron is assigned (arbitrarily) as the reference neuron—neuron A in our example. Spikes from neuron A are then treated as a reference point or time = 0 (t). From this "reference spike" we count the number of spikes fired by neuron B at various positive and negative time lags (t +/- b, b=time bin); this process is repeated for every spike emitted by neuron A. Summing the counts of spikes from neuron B, relative to the spikes of neuron A at the different delays, provides an estimate of the temporal dependence of the spikes of neuron B relative to those of neuron A. Specifically, if there is a persistent relationship such that neuron B always fires a spike 3 ms prior to those spikes fired A, it may be inferred that in general the firing of neuron A depends on that of neuron B. Similarly, if neuron B inhibited the firing of neuron A, one would expect the crosscorrelogram to be characterized by a trough around 0. However, as will be shown below, several features of the CCG limit its applicability to the study of dynamic connectivity in the nervous system.

5.2.2 Computing the JPSTH

Aertsen et al. (1989) were the first to propose and implement the joint peri-stimulus time histogram (**JPSTH**), as an alternative to estimate the functional connectivity between neurons. Several factors motivated the development of the JPSTH. First, CCGs are temporally cumulative meaning that their derivation removes any information about the time course of enhanced correlations between two neurons. Described in detail below, the correlation matrix constructed by the JPSTH directly

addresses this short coming. Secondly, given that the relationship between two neurons may change over time (e.g., from the start of a stimulus presentation the end), then the inherent averaging of the CCG may mask the relationship between the two neurons. The JPSTH in contrast, allows the user to examine this time course in great detail. Thirdly, it has been shown that the CCG, when compared to the JPSTH, is limited in its ability to detect inhibitory interactions, possibly underestimating them by an order of magnitude (Espinosa and Gerstein, 1988). Fourth, and perhaps most importantly, the mathematical derivation of the JPSTH eliminates trivial correlations induced by trial to trial variability in the firing rates of a stimulus. Given that CCG can be dominated by trivial firing rate correlations, they are 1) inherently less reliable and 2) provide less information regarding actual changes in network dynamics. Moreover, and again unlike the JPSTH, the CCG cannot provide an estimate of the interaction between two neurons with respect to a stimulus. The following section will introduce the foundations of the JPSTH and then discuss the mathematical core of its function as well as additional steps that were implemented to guard against spurious correlations.

The JPSTH can be understood simply by considering two spike trains emitted by neurons A and B in response to a stimulus. By aligning these spike trains perpendicularly along the outside bounds of a matrix (M) and drawing vertical/horizontal lines emanating from each spike that cross the matrix, the stimulus locked temporal relationship of each spike in neuron A with respect to each spike from neuron B can be revealed. Each intersecting point can then be thought of as a measure of the co-

incidence between the two spike trains. Points that fall exactly along the main diagonal represent synchronous spikes. Points which fall above the main diagonal represent incidences in which spikes from neuron A preceded those from neuron B, and vice-versa for points below the main diagonal. Averaging the coincidence counts along the main diagonal in fixed bins offset from the main diagonal, provides a stimulus locked CCG. The "strength" of the interaction between two neurons can be estimated by taking the mean around the central bins. However, several steps need to be taken to ensure true statistical dependence. These steps along with the mathematical derivation of the JPSTH will be described below.

Mathematically, the JPSTH can be thought of as a matrix with the addition of a third dimension. The first two dimensions signify the temporal interval [0,X-secs] of spike times of neuron A and B relative to the start of the trial or image presentation, with the third dimension representing the number of trials. The first two dimensions are subdivided into temporal bins (bin sizes used in the literature vary from 2msec to 70msecs). For a trial 1 sec in length with 20msec binning each dimension would contain 50 bins. This arrangement forms an evenly spaced grid along the entire dimension of the matrix, with each grid representing a count of coincident spike times from neuron A (Ti) and Neuron B(Tj). The content of each square (T i,j) is the count of coincident spike times between those two neurons at particular temporal delays (i,j). Averaging the sum of these counts (along the third dimension) provides the raw JPSTH (Eq.3 Aertsen 1989):

$$\left\langle n_{ij}(u,v)\right\rangle = \frac{1}{K}\sum_{k=1}^{K} n_{ij}^{(k)} * (u,v) \qquad \text{(EQ. 5.1)}$$

At this point, the raw JPSTH still contains contributions to the correlation counts, which are due to the shape of the product of the two marginal distributions (EQ 5.2, EQ. 4 Aersten 1989), stated otherwise the product of the two PETHs.

$$\tilde{n}_{ij}(u,v) = \left\langle n_i(u)\right\rangle\left\langle n_j(v)\right\rangle \qquad \text{(EQ. 5.2)}$$

Removing the "predicted-JPSTH" reveals whether the observed coincidence counts greater than predicted by chance (EQ 5.3, EQ 5; Aertsen 1989). Subtracting the contribution yields:

$$\begin{aligned} Dij &= \left\langle n_{ij}(u,v)\right\rangle - \tilde{n}_{ij}(u,v) \\ Dij &= \left\langle n_{ij}(u,v)\right\rangle - \left\langle n_i(u)\right\rangle\left\langle n_j(v)\right\rangle \end{aligned} \qquad \text{(EQ. 5.3)}$$

However, at this point the JPSTH still contains possible fluctuations due to background flucutations . As noted by Aertsen et.al (1998), in order to compare the JPSTHs for different stimuli or neurons, a normalization step is required in order to "a data-dependent measuring stick to arrive at a data-*independent* measure of the null hypothesis". To achieve this normalization, the JPSTH (i.e., the cross-covariance) is divided by the standard deviation of the predictor (Eq 5.4) and is given by:

$$C_{ij} = \frac{D_{ij(u,v)}}{\left\{D_{ij}(u,v)D_{ij}(u,v)\right\}^{\frac{1}{2}}} \qquad \text{(EQ. 5.4)}$$

Integrating along the diagonal and paradiagonal provides a normalized trial locked CCG.

The JPSTH calculation presupposes that the activity of neurons is stationary over repeated trials. Non-stationarities in the response can introduce spurious results in the covariogram (Brody, 1999a; Grün et al., 2003; Nawrot et al., 2003). However, Brody (1999) provided evidence that peaks in the CCG and JPSTH can be generated not only by synchronized spikes but also by covariations in the latency of the neurons response as well as excitability. To control for these factors, Brody (1999) introduced a normalization that removes any contributions to the covariogram that are due to trial-by-trial fluctuations in background firing rate. Formally, the normalization is given by:

$$V = \hat{P}_1(t) \; \hat{P}_2(t) - \left\langle \hat{P}_1(t+t_1^r) \right\rangle \left\langle \hat{P}_2(t+t_2^r) \right\rangle \qquad \text{(EQ. 5.5)}$$

5.3 Results

The hypothesis of interest is whether there exists an experience-dependent change in the "functional connectivity" between neurons. One limitation of the JPSTH is the requirement for a large number presentation for a given stimulus. However, given that some of our stimuli were only seen relatively few times and may consequently provide unreliable estimates of "connectivity estimates", an alternate approach was chosen. Instead of computing estimates of connectivity strength for each image and averaging across images in the novel and familiar categories, images were simply sorted depending on whether they were part of the novel or familiar group. The intermediate group is excluded from this analysis as even splitting the presentations into first/last

four for novel and familiar would provide too few images for reliable JPSTH estimates by having an unreliable shuffle predictor/corrector (EQ 5.5).

Three JPSTH matrices were estimated for each neuron, one for all images (independent of category), one for all novel images and one for all familiar images. JPSTHs were computed and normalized as described above. The size of bins used to compute the trial specific covariograms which make up the JPSTH varies widely in the literature from 2-70ms (e.g., Palm et al., 1988; Vaadia et al., 1995; Erchova and Diamond, 2004; Paz et al., 2009). Given the relatively sparse firing properties of neurons in the cortex, as well as their known temporal integration windows (15 - 72 ms for perirhinal neurons, as well as cortical neurons more generally (Kim and Connors, 1993; Martina et al., 2001; Moyer et al., 2002), a bin size of 20ms was chosen and coincidence counts were generated across and the entire 2 second image presentation.

Importantly, our experimental design balances the total number of image presentations between the categories. Therefore unequal numbers of image presentations were not a concern for the current analysis. Moreover, trial number is a normalizing factor in the JPSTH analysis itself, again removing this as a possible bias factor. Finally, only well isolated neurons from the same electrode were included in the analysis.

When selecting pairs of neurons, it became clear that there were significantly more hippocampal cell pairs (n = 93), compared to recordings from individual cortical regions. Consequently, cortical (PRC, TF,TLR, EC) neurons were combined across region

(CTX n = 81), allowing for a better characterization of the differences between the two populations. Results throughout this section will refer to interactions between hippocampal and cortical neurons.

Using bnCCG computed from all images presented to an animal (i.e., no differentiation between novel/familiar/intermediate images) revealed three types of interactions: uncorrelated, putative inhibitory and putative excitatory (Figure 5.1 A-C). All interactions are referred to as "putative" as their connectivity/interaction is only inferred and not directly measured.

The "strength" of the correlation between pairs of neurons was taken as the mean bnCCG values across +/- 15 bins of the bnCCG. The value of 15 bins was chosen after a visual inspection of bnCCGs revealed a variety of widths for the central peaks and troughs; some pairs had very narrow central peaks while in other case peaks were considerably wider. Figure 5.1D visualizes the distribution of correlation values for all pairs of neurons (hippocampal and cortical n = 178). The large peak around 0 (+/- .002) was chosen designated as the set of values, which would encompass "uncorrelated" neurons (Erchova and Diamond, 2004) (Figure 5.1A). Values above and below this group were assigned to the correlated (putative excitatory) or uncorrelated (putative inhibitory) group. The relative proportion of interaction types for hippocampal and cortical neuron pairs can be seen in the inset pie charts in 5.1 (D). In the hippocampus, approximately 67 % of neuron pairs fell into the "non-interacting" category, with 22% (n = 20) showing enhanced interaction and 11 % (n = 10) showing negative interactions. In

contrast, pairs of cortical neurons showed a more positive correlations (77% of pairs n = 62) and approximately 23% (n = 19) were uncorrelated.

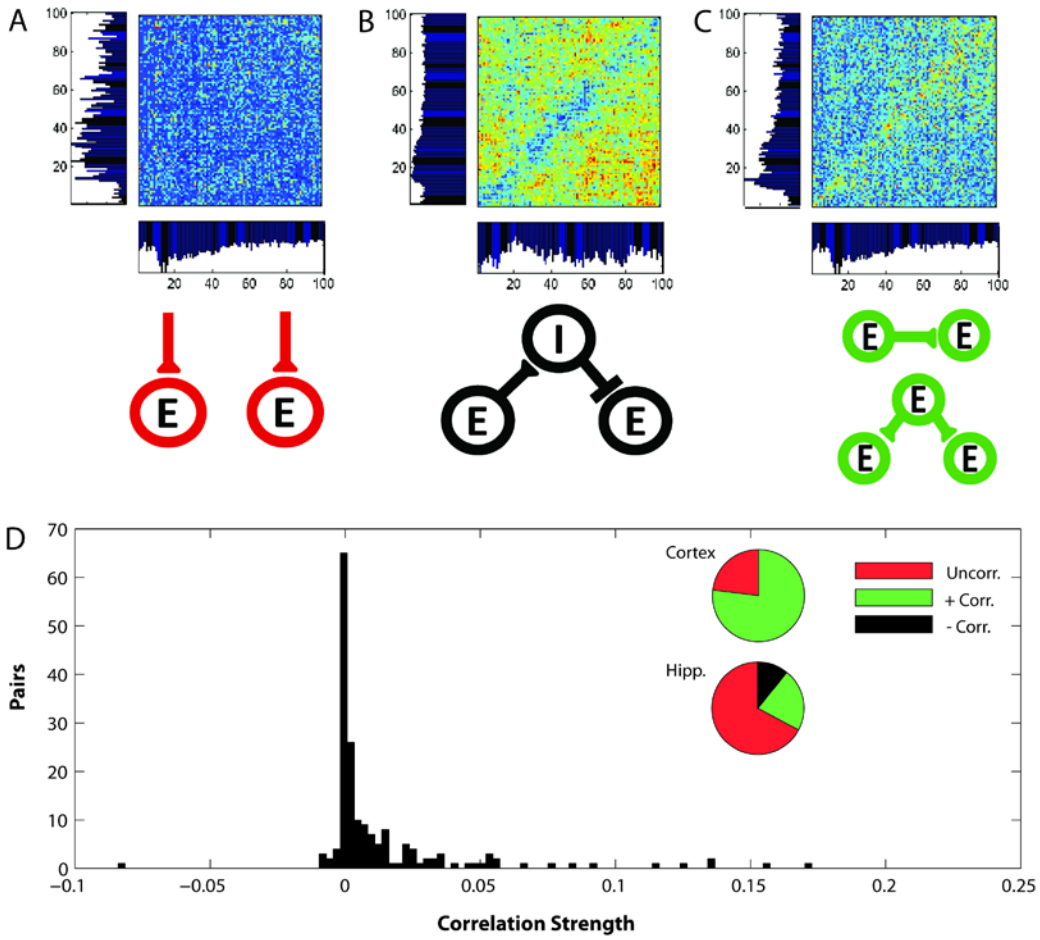


Figure 5.1 - JPSTH Types and Regional Distributions
A-C. Examples of different types of correlation types revealed by JPSTH analysis. Top - JPSTH flanked along its axes by the PETH for each of the neuron pairs. Bottom - Diagrams of putative connectivity that could produce the observed types of activity. E-Excitatory neuron, I = Inhibitory neuron. Notably the JPSTH for A and C, share a common neuron (bottom PETH) yet show very different types of correlations. Colors of the connectivity diagrams, are reproduced in inset pie charts in D. All connection types are "putative" as no anatomical verification exists. **D.** Histogram of correlation strengths for all visually responsive neurons. In set pie charts represent the relative proportion of the different interaction types observed in cortical and hippocampal recordings.

5.3.1 Experience modifies short time scale temporal correlations

To test the hypothesis that there exist an experience-dependent weakening in the functional connectivity between neurons, JPSTHs and the associated bnCCG were computed for novel and familiar images. JPSTHs were only calculated for visually responsive neurons from the same tetrode, which showed non-zero interactions in the all images condition. Wilcoxon rank sum tests suggested there was a significant difference between novel and familiar conditions for pairs of cortical neurons ($p = .02$, $n = 62$), but not hippocampal neurons ($p = .72$, $n = 30$). Comparison of the medians between novel and familiar images for cortical neurons suggested that neurons in the familiar condition are less correlated than in the novel condition.

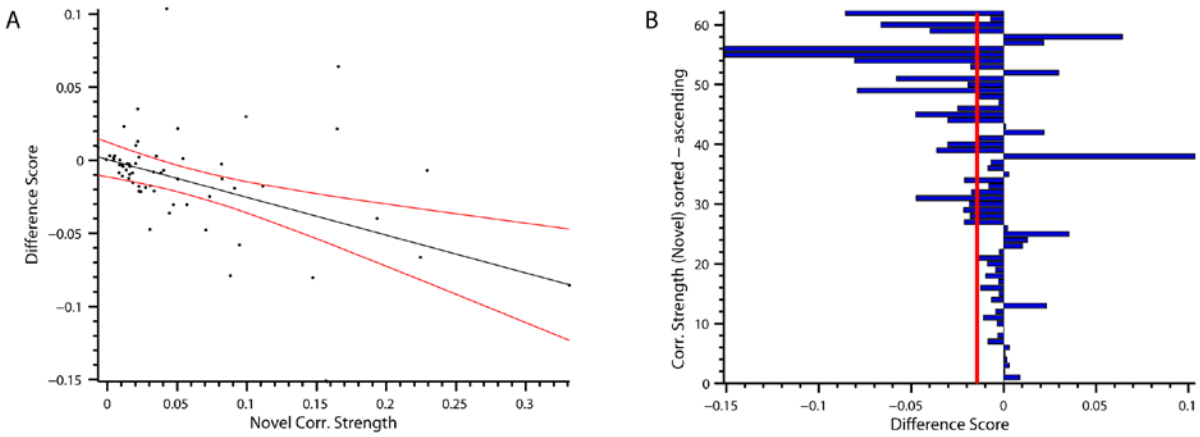


Figure 5.2 - Decreases in Functional Connectivity Strength.
(**A**) Results of a linear regression comparing the correlation strength (i.e. mean bnCCG) for each neuron pair (blue dots) in the novel condition with the difference in correlation strength between the familiar and novel conditions, revealing a highly significant negative correlation. Black line represents the linear regression, and red lines represent the error of the regression. (**B**) As in (A), visualization of the changes in correlation strength (ΔbnCCG – in text) according to how strongly neurons were correlated in the novel condition. Horizontal bars represent the change between conditions, and the sign (+/-) represents decreasing and increasing magnitudes in their temporal correlation strength. Red line represents the mean of the distribution.

To further quantify the observed difference between cortical neurons in the novel vs. familiar condition, raw difference scores were calculated for each neuron pair; where the difference is given by (ΔbnCCG = bnCCG_familiar-bnCCG_novel). This score is negative if the correlation between a pair of neurons was weaker in the familiar than novel condition and positive if the correlation between the pairs became stronger. A linear regression between the "strength" of the correlation for novel images against ΔbnCCG revealed a significant negative correlation (r^2 = .2 , p < .0001 ; slope= - 0.26; R = -.44; Figure 5.2A), indicating that pairs of cortical neurons tend to become less correlated as a function of experience. To further visualize the dynamic changes in correlation strength, pairs of neurons were sorted according to their *strength* in the novel condition and their difference scores plotted (Figure 5.2B). Figure 5.2B recapitulates the regression of 5.2A in demonstrating that on average the more highly correlated the activity between two neurons in the novel condition, the greater the change between them in the familiar condition. However, several pairs show the opposite pattern of interaction, clearly increasing their strength in the novel condition. There was no significant relationship between pairs of hippocampal neurons (r^2 = .06 , p =.19 ; slope= - 0.17; R = -.24).

5.4 Conclusion and Discussion

The present analysis demonstrates that JPSTH analysis can reveal three distinct types of temporal correlations between pairs of neurons in the medial temporal lobe. The two principal findings to emerge from this analysis are: 1) the dissociation in the

patterns of correlated activity between hippocampal and cortical neurons and 2) the decreased "strength" in the correlations between cortical but not hippocampal neurons.

The proportion of neuron pairs showing strongly correlated activity in cortical circuits is largely in agreement with previous estimates (~78%, Gawne and Richmond, 1993). In stark contrast however, pairs of CA3 neurons were largely uncorrelated (~67%). The finding of uncorrelated activity can be interpreted in two ways: First, several anatomically inspired computational models of hippocampal function (e.g., McNaughton and Morris, 1987; Treves and Rolls, 1994) have suggested that the primary function of the dentate gyrus is to orthogonalize cortical inputs from the EC and relay them to CA3. As discussed in section 2.3.5, both the dentate gyrus and CA3 can effectively orthogonalize patterns of neuronal activity when very small changes are made to an environment (Leutgeb et al., 2007). However, this interpretation of DG function has recently been challenged by studies demonstrating that different environments recruit largely the same DG granule cells (Alme et al., 2010). While the present data may be compelling from a theoretical perspective of hippocampal function, the recent challenges to this model suggest that there may exist alternative interpretations.

A second interpretation is that there exists a critical difference between experiments in rodents and the current experiment. Ensemble recordings in rodents routinely show evidence of enhanced cross-correlations between pairs of neurons (e.g., Buzsáki et al., 1992; Wilson and McNaughton, 1993; Pastalkova et al., 2008) and this

correlated activity has been demonstrated to be replayed during sleep (e.g., Wilson and McNaughton, 1994; Kudrimoti et al., 1999). However, virtually all experiments in rodents focus on spatial learning and navigation (the expression of which requires and intact hippocampus), which induce correlations between neurons due to the sequential and overlapping nature of place specific firing in the hippocampus. Hence, the absence of correlations in the hippocampus may not reflect an inherent functional property of the hippocampal network but rather reflect the lack of a spatial component in our task. Partial support for this interpretation comes from a recent study by Hori et al. (2011) that demonstrated that approximately 60% of neuron pairs in the rhesus hippocampus show enhanced cross-correlations when head-fixed animals navigate in real and virtual environments (in contrast to 22% in our data). In addition, functional imaging studies using 2DG have suggested that in the primate CA3 may not be activated by mnemonic tasks (Sybirska et al., 2000).

The second major finding presented in this chapter is the experience-dependent change in the correlation strength between pairs of cortical neurons. If the short time scale temporal correlation between pairs of neurons represents a proxy measure of connectivity between neurons, this result implies that on average, the connection between neurons tends to weaken as a function of experience (Figure 5.2B & Figure 5.3). The question becomes what are the possible physiological mechanisms supporting the observed phenomenon.

From a physiological perspective, the change in the correlation strength would most likely be driven by an LTD-like mechanism. In the perirhinal cortex, the expression of LTD is dependent on the activity of the AP2 clathrin adapter protein, which associates with the GluR2 subunit of AMPA receptors and facilitates their internalization (Carroll et al., 1999; Beattie et al., 2000; Man et al., 2000). Blocking the association between AP2 and GluR2 via viral peptides *in vitro* abolishes LTD while leaving LTP intact (Griffiths et al., 2008b). When the association between AP2 and Glur2 is blocked *in vivo* via direct injection of a viral peptide into the PRC of behaving animals, recognition memory performance is severely impaired. The authors suggested that this effect on the expression of LTD could block response decrements, which their group has previously championed as the neural correlate on which animals base their familiarity discriminations (See 2.3.1 for the criticisms of this view). However, there is no *in vivo* electrophysiological evidence that links a blockade of LTD to changes in response decrements, and in fact, data from primates suggests that recognition memory can be impaired in the absence of a change in response decrements (Miller and Desimone, 1993). Taken together, the current data warrant a rethinking of this interpretation.

An alternative consequence of LTD blockade would be that populations of neurons could no longer weaken their connections. As discussed in chapter 1, a representation of a stimulus at the neural level is not only the pattern of active neurons but also the correlations between neurons. Accordingly, a network of interconnected neurons (such as cortical module) may suffer from a cross-talk as the number of items

or traces to be stored increases (MacGregor and Gerstein, 1991). Hence, it is not the absence of a response decrement that interferes with the expression of recognition memory. Rather, it may be that the pattern of correlated activity between neurons is too similar between competing representations, leading to false recall, and consequently poor recognition memory performance.

An extension of this view is that it is possible that the decrease in correlation strength is the result of a reduced "driving" response from upstream cortical areas such as TE/TF. Specifically, as the current results and published data from Freedman et al. (2006) indicate, both TF and TE (the major inputs to PRC 35/36) show experience-dependent narrowing of their tuning profiles. Hence, it would be the connections between regions that become more specific. Interestingly, Yoshida et al. (2003), using a sophisticated combination of recordings and different retrograde tracers, demonstrated that when rhesus monkeys learn paired-associate tasks there occurs an experience-dependent retraction in the connections between neurons that are sensitive to learned pairs. The present data may then be a direct complement to Yoshida et al. (2003), by demonstrating that modification of the "functional connectivity" between neurons can occur in the absence of stringent behavioral training. As suggested above, the present results represent an important bridge to the interpretation of effects seen at the molecular and cellular, and behavioral levels—providing a window into the functional consequences of LTD-like processes on neural networks *in vivo* during active behavior.

CHAPTER 6- CORRELATION OF GAMMA OSCILLATIONS AND CELL ASSEMBLY FORMATION

6.1 Introduction

Chapters 4 and 5 demonstrated that experience can modify the representation of objects by populations of neurons and the functional connectivity between them. However, neither of these findings addresses a more fundamental question of how activity in the nervous system becomes correlated in the first place. As discussed in chapters 1 and 2, one candidate mechanism that could orchestrate the activity of neurons are oscillations in the local field potential. Gamma oscillations, in the range of 30-100 Hz, are a particularly prominent oscillation, observed in many species, and have has been implicated in a variety of cognitive processes ranging from attention to feature binding and working memory. This has suggested to some that gamma oscillations may represent a highly conserved mechanism by which neural networks are able to coordinate their activity (e.g., Buzsáki, 2006; Fries et al., 2007).

Gamma oscillations have been demonstrated to arise from the synaptic activity of networks of inhibitory interneurons (e.g., Freund and Buzsáki, 1996; Hájos et al., 2004; Bartos et al., 2007). *In vitro* studies of gamma oscillations demonstrate that the somatic compartment of principal neurons in the hippocampus shows a large increase in the number of Inhibitory Post Synaptic Potentials (IPSPs) at gamma frequency when compared to when no gamma oscillations are detected (e.g., Whittington and Traub, 2003). Moreover, patch recording studies *in vivo* and *in vitro* demonstrate that gamma oscillations, or electrical stimulation at gamma frequencies, enhance the precision of

action potential firing (Fellous and Sejnowski, 2000; Fellous et al., 2001; Tiesinga et al., 2001, 2008; Klausberger et al., 2003; Tukker et al., 2007b). The significant spatial extent of these interneurons allows them to contact a large number of spatially distributed principal neurons (e.g., Buzsáki et al., 2004; Somogyi and Klausberger, 2005). From a theoretical perspective then, gamma oscillations are thought to provide a timing signal to large populations of neurons, and that neurons can use this signal to synchronize their activity (Singer, 1993; Gray, 1994; Engel et al., 2001b, 2001b).

Specifically, it is hypothesized that gamma oscillations are responsible for generating "gamma coherent cell assemblies" (**GCCA)**—networks of neurons whose activity is entrained at gamma frequencies. However, the vast majority of studies either consider only the power of the oscillation or the relationship between the spikes emitted by a single neuron in relationship to an ongoing gamma oscillation. While these approaches may be suggestive of GCCA, a more appropriate measure would be one that can quantify whether neurons themselves tend to be more correlated during gamma oscillations (Csicsvari et al., 2003). Section 6.2.2 will highlight how measures of gamma assemblies inferred from spike-lfp relationships can be misleading. 6.2.3 will discuss how the information contained within the JPSTH can be used to better characterize the existence of GCCA.

Previous studies in primates have linked increased gamma oscillations in the hippocampus with performance on a mnemonic task (Jutras et al., 2009). Specifically, the authors demonstrated that the magnitude of the coherence between spikes and

gamma oscillations at encoding time was predictive of subsequent recognition performance. Similarly, studies in humans have demonstrated that the magnitude of coherence between gamma oscillations in the hippocampus and rhinal cortices is associated with memory formation, suggesting that gamma oscillations coordinate the activity between these regions (Fell et al., 2001). Bauer et al. (2007) demonstrated that, in rodents, gamma oscillations are responsible for coordinating spiking activity between rhinal cortices (PRC/EC) and the basolateral amygdala during learning of a trace conditioning task.

The analyses presented in section 6.3 were designed to investigate whether in primates, similar to rodents, gamma oscillations are implicated in coordinating the activity between neurons and whether there exists an experience-dependent modulation of gamma oscillations. Section 6.4 will summarize and discuss the findings of 6.2 and 6.3.

6.2 General Methods

6.2.1 Quantification and extraction of gamma filtered field potentials.

As described in chapter 3, local field potential recordings (LFP) were continuously recorded from one channel of each tetrode. The reference electrode for EEG (as for the units) was a tetrode located above the level of the hippocampus. With two exceptions all analyses for gamma oscillations were implemented using custom written software in Matlab (Mathworks, Cambridge, MA). Filtering of the local field potential was implemented with the eegfiltfft function from the EEGlab toolbox (Delorme and Makeig,

2004). This function utilizes an inverse FFT filter to estimate spectral power within a pre-defined frequency range. Moreover, 2D time frequency representations (2D-TFR) were constructed using Ole Jenson's traces2TFR method which can be found in the *4DToolbox* data analysis tool box (http://neuro.hut.fi/~tanzer/d4d/). Briefly this method decomposes field potential data into discrete frequency bands and utilizes Morlet wavelets to estimate power within a particular band. This procedure is repeated for all frequency bands over a given step size, yielding a full characterization of spectral power locked to the stimulus. To estimate spectral regions of interest, 2D trial averaged spectrograms were constructed for all images, as well as for novel and familiar images separately (Figure 6.1). These plots revealed two significantly elevated regions of activity, one between approximately 30 Hz to 50-55Hz and one from 70 Hz to about 100 Hz.

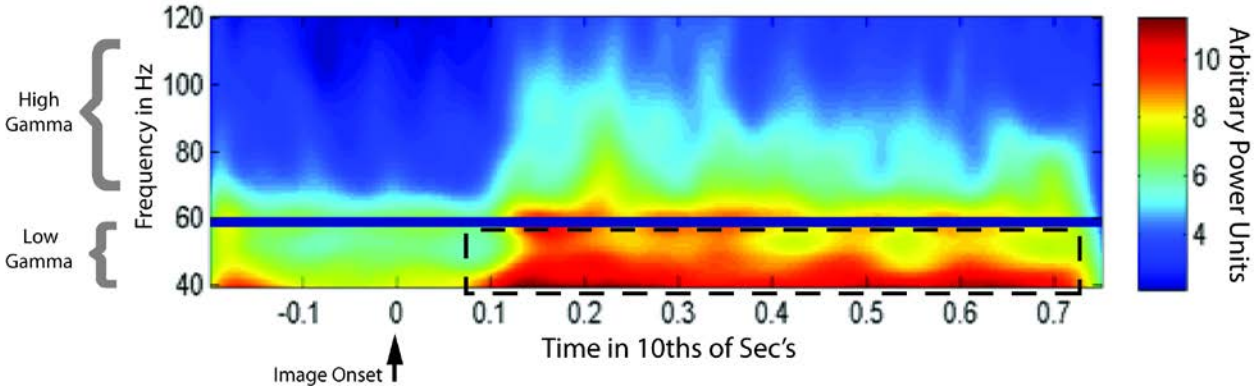


Figure 6.1 - Gamma oscillations in PRC.
Stimulus locked two dimensional time frequency decomposition recorded from one tetrode channel on one day in the PRC. Note the two separate regions of elevated power, one highly distinct region between 40 and 55 Hz, and another less distinct region above 60 Hz. Trial specific gamma power was estimated in the temporal and frequency portion indicated by the black dashed line.

For reasons to be discussed below (6.2.2), the power of gamma oscillations was estimated only in the range from 35-55 Hz. The raw continuous LFP trace was filtered at this range for the entirety of the recording session before any further processing and trial alignment took place. This ensures that no signal artifact is introduced due to edge transients. Post filtering, blocks of gamma filtered LFPs (**gLFP**) were extracted starting from 100 ms post stimulus onset to 700 ms post stimulus onset. This time window was chosen based on what appeared to a human observer as the offset of the gamma response.

6.2.2 Traditional methods for assessing gamma oscillations and their short comings

The relationship between spikes and the ongoing field potential are generally measured by correlating the position of a spike relative to the phase of an oscillation. Presently, the phase of the gLFP was estimated by decomposing the signal into a discrete-time analytic signal via Hilbert transform. The Hilbert transform produces a complex valued signal in which the real components represent the signal amplitude and the complex values represent phase information (Hilbert, 1953; Cohen, 2008). Conversion of complex values to radians and then to degrees provides a highly accurate estimation of the instantaneous phase of an oscillating signal.

The first approach to this analysis was to construct a histogram of spike phase preference. Specifically, for every spike a neuron fired in response to an image, its instantaneous phase was found and added to an ongoing count (Figure 6.2A). Figure 6.2

is a representative example of a neuron which showed a highly reliable spike/phase relationship with the spike preferentially firing near the peak of the gamma oscillation. The magnitude of the effect suggested that gamma modulation of the spiking activity should be visible in the spike-triggered-average (**STA**).

STAs in addition to spike/phase plots are an additional measure with which the relationship between an oscillatory signal and an oscillation can be assessed. 100ms epochs of the gLFP signal were extracted around the time of each spike and averaged. The resulting plots (Figure 6.2B) reveal the extent of the relationship between the two signals. Figure 6.2B, as 6.2A, shows that spikes (time 0) preferentially align their activity to the peak of gamma oscillations, suggesting a significant synchronization of spikes and gamma oscillations.

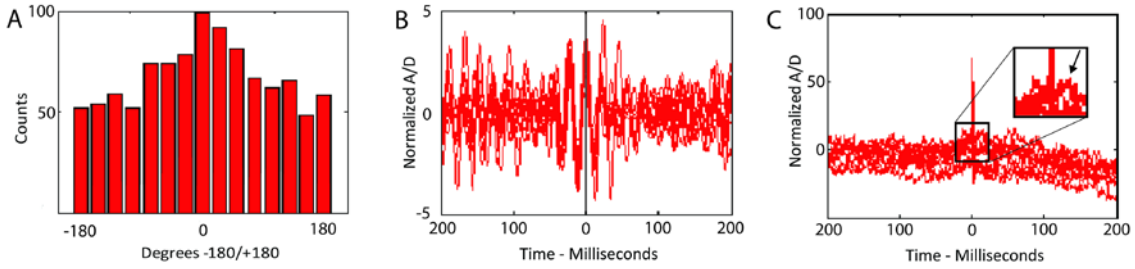


Figure 6.2 - Spike-Phase relationships.
Action potential induced correlation of spike-phase relationships. (**A**) Histogram of spike-phase preference in relationship to broadband gamma filtered LFP signal (30-120 Hz). A significant proportion of spikes occur at or near 0 phase (i.e., the peak of the gamma oscillation. (**B**) Spike triggered average of broadband gamma frequency filtered LFP (30-120 Hz), where time 0 represents the occurrence of a spike. This plot seemingly demonstrates, as in A, a strong preference for spikes to occur at the peak of the gamma filtered signal (grey line), suggesting robust synchronization between spikes and the local field potential. (**C**) Spike triggered average of the raw LFP signal, with clear spike bleed-through into the LFP signal. The observation of a prominent action potential transient along with spike-phase preference shown in A & B, suggests that the effects observed in A&B are due to this transient.

Once more, the magnitude of the effect in these plots suggested that the spike/phase relationship should be obvious in STAs of the raw LFP signal. Importantly, STAs on raw LFP traces can allow one to determine the precise frequency of gamma oscillation modulating the spikes without a priori designating a frequency range (Siegel and König, 2003). Troublingly, this figure (6.2 C) revealed that a proportion of individual spikes "bled through" into the LFP signal—causing a sharp transient in the signal. Moreover, there is little, if any, evidence for actual gamma related activity in the STA (Figure 6.2 C inset, black arrow). The presence of individual spikes, or any sharp transient, in the raw LFP signal is analogous to the presence of a Dirac function. Dirac functions inherently have power in all frequencies and are centered at zero phase (Dirac, 1930; Kramer et al., 2008; Ray and Maunsell, 2011), a feature particularly detrimental to LFP analysis, as in our case it clearly explains the observed phase alignment in Figures 6.2 A&B.

It is likely that the relative influence of a Dirac function on a power estimate would be magnified at higher frequencies where the absolute power of the signal is already low. The influence of such transients is significantly less in lower frequency bands given that the power of those oscillations is much larger thereby minimizing the effects introduced by transients. Importantly, many studies of gamma oscillations attempt to work around this artifact by sampling the LFP from a nearby neighboring electrode (e.g., Womelsdorf et al., 2007; Fries et al., 2008; Jutras et al., 2009). The spatial extent of the local field potential is on the order of several 100 microns (e.g., Xing

et al., 2009; Lindén et al., 2011); although the spatial reach can depend partially on the cortical state (Destexhe et al., 1999; Nauhaus et al., 2009). Due to the different spacing between our tetrodes, we cannot use this approach.

To determine the relative contribution of spikes to the LFP signal and whether any measure of gamma could be reliably identified as being non-spike in origin, two dimensional-spike triggered average-time frequency representations (2D-STA-TFRs) were constructed. This method effectively replicates our stimulus locked measures of frequency contributions (Figure 6.1). However, rather than using image onset as our aligning event, individual spikes were used. As in standard STAs, for every spike +/- 200 ms of raw LFP signal was extracted. For each individual STA one 2D-STA-TFR was generated. 2D-STA-TFRs were estimated from 20Hz to 140Hz. Frequencies below 20Hz were not evaluated due to concerns that the short temporal window of the LFP snippet could induce edge artifacts. Individual 2D-STA-TFRs were averaged, to construct one 2D-STA-TFR per neuron across all spikes (Figure 6.3 A).

The resulting figure clearly reveals a spike locked (i.e., 0 ms) narrow band of increased power from 60-100 Hz and from 120 Hz upward introduced by the spike transients. Interestingly, this figure appears to also capture what is likely to be an actual gamma modulation in the 35-55 Hz range. As noted above, the frequency window for subsequent analysis of gamma oscillations was chosen based on the results of this analysis. This finding was confirmed and extended by two independent groups shortly after this analysis was conducted (Ray and Maunsell, 2011; Zanos et al., 2011). While

the above draws attention to technical issues which must be considered when performing LFP analysis, it does not address the earlier concern that this type of analysis does not actually demonstrate the existence of GCCAs.

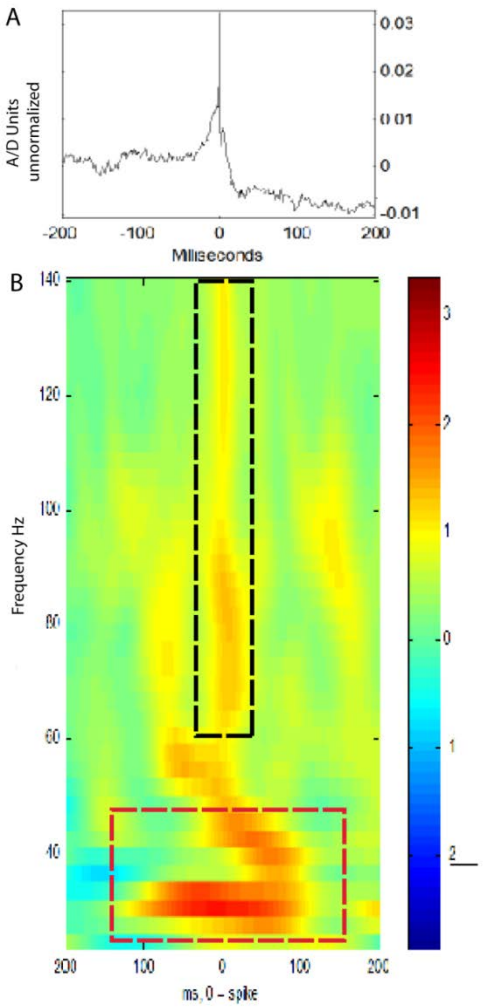


Figure 6.3 - Mapping the frequency extent of spike contamination.
(**A**) STA average of raw LFP signal for spikes during image presentation. Prominent in this figure are 1) the spike contamination, clearly visible at t=0 as well as 2) increase in signal amplitude around ~ 30 ms prior to 0, possibly associated with an ongoing gamma oscillation. (**B**) **2D-STA-TFR** (two dimensional-spike triggered average-time frequency representation) with two prominent regions of elevated power: 1) Narrow spike locked increase in "gamma" power above ~ 60 Hz (black dashed box) and 2) Increased gamma power between ~30 to 55 Hz (red box) likely corresponding to the slower transient seen in (**A**).

6.2.3 JPSTH approach to studying GCCAs

The principal feature of neurons participating in a cell assembly is that their activity should be temporally correlated. Gamma oscillations are often suggested to be the physiological mechanism by which the brain solves the "binding problem", that is linking anatomically disparate neurons participating in the representation of a stimulus and whose joint activity comprises the whole of the object (Tallon-Baudry and Bertrand, 1999). Multi-unit recordings in rodent hippocampus have demonstrated that gamma oscillations can enhance the peak of CCG, suggesting enhanced connectivity between neurons. Moreover, in a cross-species study Womelsdorf et al. (2007) demonstrated that multi-unit activity between proximate recording sites is preferentially synchronized at gamma frequencies. These studies however, only address the generalities of gamma oscillations and neuronal connectivity, but fail to address the more specific hypothesis that the correlated activity between neurons should be higher when gamma power is higher and that gamma power should be highest when a stimulus is being first encoded (i.e. when an image is novel). This set of questions lends itself perfectly to analysis via the JPSTH.

6.3 Results

6.3.1 Gamma coherent cell assemblies in Cortex

To determine whether gamma oscillations are associated with increased functional connectivity between neurons, average gamma power was calculated for every image on a given recording day. Within each day, gamma values were divided into

trials associated with the lowest 30% in terms of gamma power and the highest 30%. As described in 5.2.2, JPSTHs were computed for well isolated visually responsive pairs of neurons. For each pair of neurons two JPSTHs were calculated, one for trials associated with the 30% of trials with the highest gamma power and another with the bottom 30% of gamma power. As before, “strength” of the connectivity between neurons was assessed by taking the average of the Brody normalized cross-correlogram across +/- 15 bins of the center. As in chapter 5, CA3 neurons were assigned to the category "hippocampus" while neurons from regions TF, PRC, EC and TLR were assigned to the "cortical" category.

Figure 6.4 shows the correlation strength between hippocampal (6.4A) and cortical (6.4 B) neurons during trials high (red) and low (grey) gamma power. Cortical neurons showed a significant difference between novel and familiar conditions (Wilcoxon rank sum test , $p = .013$, $n = 89$), but hippocampal neurons did not (Wilcoxon rank sum test , $p = .806$, $n = 97$).

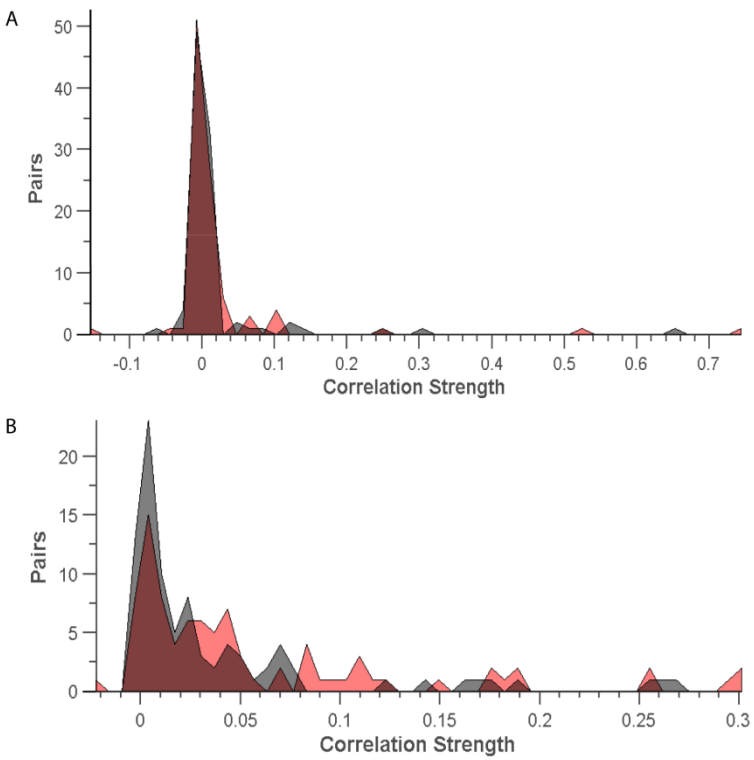


Figure 6.4 - Gamma coherent cell assemblies.
JPSTH based measure of gamma cell assembly formation. Red shaded areas- high gamma power (top 30%), Slate shaded areas correspond to low gamma power (bottom 30%). (**A**) Correlation strengths for pairs of neurons sampled from the CA3 region of the hippocampus, showing no modulation by locally recorded gamma oscillations. (**B**) Correlation strengths for cortical neurons showing a small, albeit significant increase in their temporal correlations.

6.3.2 Enhanced Gamma Oscillations for Novel Stimuli

A central prediction of the gamma/binding hypothesis is that these oscillations should be enhanced during the encoding of a stimulus, which in the present experiment corresponds to novel stimuli. Jutras et.al (2009) and Fell (2001), have demonstrated that gamma oscillations within the hippocampus and between hippocampus and across rhinal cortices are enhanced during the encoding phase of a recognition memory task. To test whether gamma oscillations showed similar dependencies, we compared the normalized magnitude of gamma oscillations between novel and familiar conditions.

To compare the power of gamma oscillations across days, the gLFP signal for each day was converted to z-scores. Mean gamma power was computed for each day in the novel and familiar category. As above, data were grouped into "cortical" and "hippocampal" groups. For cortical neurons there was a significant difference between novel and familiar conditions ($Mean_{novel}$=.11, $Mean_{familiar}$ = .09; $t(256) = 2.22$, $p = .021$). However, there was no significant difference for hippocampal neurons ($Mean_{novel}$=.0479, $Mean_{familiar}$ = .0486; $t(102) = -.07$, $p = .944$). These data are largely consistent with previous reports of the role of gamma oscillations during encoding, although we fail to replicate the findings of Jutras et.al (2009). The possible reasons for this are discussed below. The reader may note that the normalized gamma values appear relatively small, however these values are consistent with previously published data (e.g., Chrobak and Buzsáki, 1998; Headley and Weinberger, 2011).

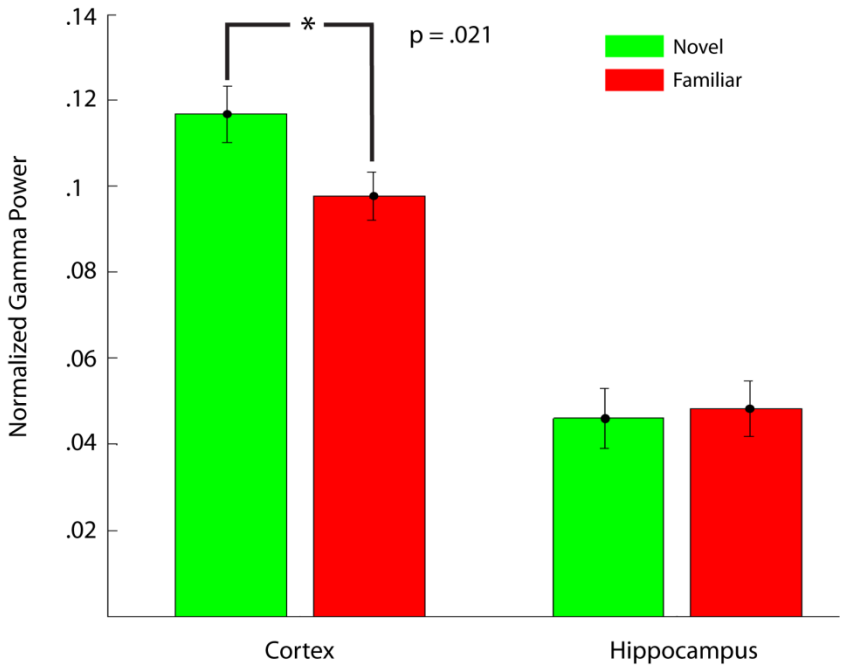


Figure 6.5 - Gamma oscillations and stimulus novelty.
Comparison across days of the mean amplitude (strength) of gamma oscillation recorded in (rhinal) cortex and the hippocampus (CA3); error bars-standard error of the mean. Gamma oscillations in rhinal cortices are enhanced during the presentation of novel images (green bars) compared to familiar images (red), but not in hippocampus.

6.4 Conclusions

High frequency oscillations in the local field potential occur in a numerous species and have been linked to attentional processes and mnemonic performance (for an excellent review see: Buzsáki (2006)). The data presented in the chapter above add several new facets to our understanding of gamma oscillations. First, several recent studies as well as data presented in the methods section of this chapter, have called into question findings related to gamma oscillations, especially those found at higher frequencies (Ray and Maunsell, 2011; Zanos et al., 2011). Briefly, contamination of the field potential signal by sharp transients, be they action potentials or electrical artifact from reward delivery systems, can produce spurious estimates of gamma power. This

type of artifact is not limited to intra-cranial recordings as it has been shown that EMG activity associated with microsaccades can influence scalp gamma recordings as well (Yuval-Greenberg et al., 2008, although see Melloni et al., 2009; Bosman et al., 2009). Figure 6.3 demonstrates that the extent (in frequency space) of spike contamination is particularly prominent in LFP signal above ~ 60Hz.

Gamma oscillations have been proposed to be crucial to the precise temporal organization of neuronal ensembles and more broadly, are proposed as a solution to the binding problem. Studies in both rodents and primates have begun to directly correlate gamma oscillations with enhanced communications between neurons (Csicsvari et al., 2003; Womelsdorf et al., 2007). The second contribution of this chapter is a demonstration that gamma oscillations recorded from regions within rhinal cortex (EC,TF,PRC) of behaving macaques appear to enhance the coordinated activity between pairs of neurons, and moreover that gamma oscillations are higher when animals view novel images (i.e., encoding) than when viewing familiar images.

Similar to our finding of enhanced correlations between neurons, Jutras et al. (2009) showed that increased synchronization between unit activity and gamma oscillations in the hippocampus during the encoding phase is positively correlated with subsequent recognition memory performance. Implicit in the finding of that study is that gamma oscillations are preferentially enhanced during encoding, but not during the subsequent recognition trial. However, no values for gamma power or unit-gamma

coherence are reported for the recognition trials, making it impossible to compare between the current data and the study of Jutras et al.(2009).

In summary, the majority of studies, the present data included, indicate a robust correlation between an animal's behavioral state or performance on a behavioral task and increases in gamma oscillations. Given these correlations, the question becomes what is the mechanism by which gamma oscillations facilitate the encoding of a stimulus?

Novel environments (e.g., Miranda et al., 2000; Giovannini et al., 2001) as well as encoding of a stimulus (e.g., Hasselmo et al., 1996; Rokem et al., 2010) are linked with selective increases in acetylcholine and blockade of cholinergic receptors leads to deficits in recognition memory performance (e.g., Miller and Desimone, 1993; Warburton et al., 2003). Interestingly, the amplitude of gamma oscillations in the somatosensory cortex of rodents is known to be positively modulated by agonism of the cholinergic system (Buhl et al., 1998). Moreover, application of cholinergic agonists to hippocampal slices is known to enhance the expression of LTP. Critically then, given the co-occurrence of all of these factors, it is difficult to determine the direction of causation.

CHAPTER 7 - SUMMARY OF FINDINGS AND CONCLUSIONS

7.1 Summary of salient observations

The data presented in this dissertation extend our understanding of how the primate nervous system can change in response to experience, even in the absence of explicit behavioral instruction or reward. Moreover, our data offer a new perspective on an old debate regarding the mechanism underlying recognition memory.

1. Experience-dependent changes in the specificity of neuronal responses have been demonstrated across multiple brain regions and species (**Chapters 1 and 2**). Specifically, experience is believed to drive a reduction in the total number of stimuli a neuron responds to—the potential benefits of this process are two-fold. 1) Reducing the overall number of stimuli a neuron responds to can increase the storage capacity of a given neural network; 2) this increase in specificity can result in a decrease in the overlap between similar representations, ensuring accurate recall. The results presented in **Chapter 4**, extend our understanding of tuning in the medial temporal lobe by demonstrating that in the absence of explicit behavioral demands, only regions up stream of the PRC show enhanced specificity to familiar responses (**Figure 4.3**). Moreover our data demonstrate that when the responses of neurons are used as naïve classifiers, only responses from area TF are able to detect stimuli from the familiar category more reliably (**Figure 4.6**). The dissociation between the lack of tuning in PRC and Hippocampus with the presence of tuning in upstream cortical regions, suggests

a revision of the notion that enhancing the specificity of neuronal responses is ubiquitous in the nervous system. A revised version of this hypothesis needs to state that that tuning is principally a feature of primary sensory and unimodal association areas. A similar process could be highly detrimental in polymodal association areas, as it could limit the ability for these regions to construct associations between different stimuli.

2. A previous study in primates had demonstrated that hippocampal neurons can show experience-dependent sharpening of their tuning profile (Yanike et al., 2004), a finding not replicated by the current analysis. A principle difference between the current study and that of Yanike et al. (2004) was the use of a measure based on information theoretic principles to determine selectivity, referred to as a "selectivity index" (SI). However, the SI measure does not take into account whether or not a neuron's response to a given stimulus actually passes a threshold above which the change in firing rate would be considered statistically significant. In contrast, the approach taken in this dissertation is based on a simple Tukey post-hoc HSD, allowing us to determine precisely which image a neuron was selective for. An analysis between these two measures revealed no significant relationship between the SI measure and the Tukey-HSD measure (**Figure 4.9**).

3. As encapsulated by the paraphrase of D.O Hebb, the formation of memory depends not only on the activity of individual neurons, but also on the activity *between* them. Specifically, the emphasis in the context of this dissertation is on the enhancement of connectivity between neurons. However, as discussed in **Chapter 1**, this enhancement may be detrimental in the long run, as its logical conclusion is a complete "wiring together" of the nervous system—a clearly maladaptive strategy. Numerous molecular and physiological studies have begun to reveal the existence of plasticity mechanisms which counterbalance the persistent wiring together (**Chapter 2.3.1**). However, how and whether these processes manifest in primate brain has been completely unexplored. The results presented in **Chapter 5** demonstrated that using a functional connectivity analysis (JPSTH), multiple single-unit recordings can allow us to discover the different types of temporal interactions between neurons. In line with the hypothesis that effective encoding should be associated with a decrease in connectivity between neurons, and molecular data from rodents demonstrating that blocking the expression of LTD interferes with recognition memory performance, these results showed that, on average, neurons are less correlated (i.e., connected) for familiar stimuli than for novel stimuli (**Figure 5.2** and **5.3**).

4. The analysis and quantification of field potentials relies largely on spectral filtering to determine their behavioral correlates. However, the data in **section**

6.2 illustrated that a common method used to quantify field potential oscillations and the relationships of these oscillations to single unit activity may be significantly confounded by the presence of spikes in the field potential signal. It was demonstrated that the extent (in frequency space) of this contamination can be estimated via two dimensional-spike triggered average-time frequency representations (2D-STA-TFR) (**Figure 6.3**). This finding should warrant a serious reconsideration of the interpretation for the functional role of high gamma oscillations.

5. Gamma oscillations have been proposed to synchronize spatially distributed groups of neurons in order to represent a stimulus. Critically however, most studies have focused on studying the correlation between gamma oscillations and single neurons. The analysis in this dissertation took an alternative approach and estimated the activity between neurons. Gamma power was strongly correlated with enhancements in the functional connectivity between neurons (**Figure 6.4**), providing a more direct line of evidence in support of the gamma synchronization hypothesis.

7.2 Relationship to the previous literature

7.2.1 Implications for mechanisms supporting recognition memory in the primate MTL

Recognition memory is the ability for an animal to determine whether a presented stimulus is being encountered for the first time, or whether it has been previously experienced . Studies in rodents (Zhu et al., 1995, 1997), primates (Xiang and Brown, 1998; Hölscher et al., 2003; Jutras and Buffalo, 2010b) and humans (Rutishauser et al., 2006; Viskontas et al., 2006) have attempted to link both decreases and increases in the firing rates of neurons in PRC, EC, TE and hippocampus, as the mechanism by which the brain encodes the relative novelty/familiarity of a stimulus (i.e. recognition memory). The proportion of visually selective neurons showing a response decrement is surprisingly large, for example Xiang and Brown (1998) found that more than 70% of visually responsive PRC neurons showed a response decrement. In striking contrast however, the analyses presented in **Chapter 4**, found no evidence for neurons being exclusively tuned to either familiarity or novelty of a particular stimulus. The complete absence of a "recognition memory" signal compared to a signal carried by more than 70% of neurons is an extremely large discrepancy warranting further consideration.

To begin, the role of response decrements as relaying a recognition memory signal can be challenged on several fronts. For example, direct injections of scopolamine into PRC or TE potently disrupts performance on a recognition memory task, however neural firing rates remain unchanged (Miller and Desimone, 1993). Moreover, virtually all subsequent follow-up studies utilizing pharmacological inactivation in rodents, fail to

pair single unit recordings with the pharmacological manipulation used to induce a deficit. For a full discussion on the criticisms of response decrement data, see section 2.3.1 . In addition, most studies focus solely on the detection of "recognition memory signals", but do not consider whether or how neurons are actually tuned to the different experimental stimuli. Failure to fully examine the response characteristics of individual neurons significantly limits the interpretability of those results.

In addition, similar to the criticisms raised in **section 4.3** the mathematical approach used for analysis can be significantly misleading. For example, a large number of "decrementing" studies report a "percent change". This means that a change in rate from 1Hz (baseline) to 3Hz (novel condition), this threefold increase would register as a 200% relative change accordingly. This seemingly impressive amount however, may be meaningless computationally given the high rates of synaptic failure and background noise of the system. The origin of small increases in firing rate is discussed in more detail in section 7.2.2. While compelling, studies of response decrement in relation to recognition memory are largely correlative.

Finally, that response decrements reflect recognition memory signals can be seen as being in conflict with several theoretical proposals of information encoding which posit that when new representations are generated in cortical circuits, the constituent neurons undergo an experience-dependent change so as to maximize the encoding efficiency (Marr, 1971b; Amari, 1989; Desimone, 1996; Zhang and Sejnowski, 1999). Colloquially this experience-dependent change in the specificity of responses is

referred to as a "tuning" of a representation. Briefly, in this view, a stimulus is encoded in a highly distributed and non-overlapping (in respect to other stimuli) set of neurons. Experience then modifies the representation of that stimulus at the neuronal level by eliminating individual neurons from the representation (**Chapter 1 & 2**).

The data from this dissertation, and other studies, support an anatomically restricted view of tuning (**section 4.3.4**). Specifically, it appears that only neurons upstream of the PRC show an experience-dependent tuning in their representations (e.g., Freedman et al., 2006). Important in the present context, in the tuning framework, there is no explicit encoding novelty/familiarity or familiarity signal in the MTL, rather rate differences between novel vs. familiar images may be strictly the result of a tuning process and only reflect the difference in how the ensemble of neurons represents the stimulus. Extending logically from this view, it may be hypothesized that a deficit in recognition memory is due to ambiguous/overlapping representation between two stimuli at the neural level (Desimone, 1996). This prediction is in line with recent results from both perirhinal cortex and hippocampus as being involved in perceptual discriminations of highly similar (i.e., ambiguous) stimuli (Murray and Bussey, 1999; Bussey et al., 2002; Bartko et al., 2007).

7.2.2 Dopaminergic novelty signaling

As discussed in 7.2.1, the significance of recognition memory signals in the temporal lobe of humans, primates and rodents remains controversial. Nevertheless, the ability to detect whether a stimulus has been previously encountered makes sense

from an evolutionary perspective. An important component of novelty detection (or mismatch detection, as implied by the tuning hypothesis) is the ability for an organism to decide when a novel stimulus is worth orienting towards. Orienting decisions may, in part, be based on the salience of a novel stimulus (e.g., Gati and Ben-Shakhar, 1990; Downar et al., 2002). Importantly however, we should consider two types of novelty. The first kind can be thought of as occurring the very first time an organism experiences an object (e.g., a chair). However, it may also be the case that subsequent experiences with chairs can also be perceived a "novel", when an organism encounters a novel type of chair (e.g., an Eames lounger), that this is also While the first type of encounter may be highly salient, the second type is less likely to be highly salient; unless perhaps the organism has a preexisting interest in chair design. Moreover, it may be argued that novelty preference is only expressed for items from categories that the subject has learned are associated with positive (or negative) feedback. It may be argued that learned salience may be a significant factor in the development of novelty preference.

Mesolimbic dopamine (**DA**) signals have long been associated with both the detection of the salience of stimuli and dopamine levels have been shown to increase in response to novel stimuli (Schultz, 1998; Bunzeck and Düzel, 2006). Important in the present context, animals enrolled in behavioral or neurophysiological testing are virtually always placed under modified dietary regiments (i.e. food/water restriction) in order to incentivize the learning of a task. Consequently, stimuli or other aspects of the task themselves can become highly incentivized, in other words predictive of reward— a

known driver of dopamine release (Berridge and Robinson, 1998; Schultz, 1998; McClure et al., 2003). The engagement of the dopaminergic system in these tasks raises serious questions regarding recognition memory signals for two reasons.

First, dopaminergic signaling has now been shown to be composed of two components. A fast glutamatergic response and a slower dopaminergic response (Sulzer and Rayport, 2000; Lavin et al., 2005; Lapish et al., 2006). The ramifications of this are readily apparent if we consider, for example, a serial recognition task such as the one utilized by Xiang and Brown (1998). Animals must make a behavioral response indicating whether a stimulus has been previously seen or not. In this case, responding accurately (i.e., "seen previously") results in delivery of a juice reward. Over time, animal learn a novel stimulus can signal reward delivery—a well established factor which increases the activity of dopaminergic neurons. Changes in, for example, the firing rate of PRC neurons are not likely to be detecting stimulus novelty, but rather may be reacting to a temporary drive from the mesolimbic dopaminergic system. The observed "response decrements" then would be a decrement back to a baseline rate before the glutamatergic signal from dopaminergic neurons. Thus, the decrement in firing rate should be more accurately referred to as a decrement following an initial glutamate dependent increment.

Secondly, dopamine has been shown to be a potent regulator of synaptic plasticity (e.g., Frey et al., 1990; Centonze et al., 1999; Li et al., 2003). Coupled with the transiently enhanced firing rate of neurons mediated by (1) stimulus representation and

(2) rate increases from the glutamatergic component of DA signaling, it is possible that the brain of an organism "learns" to show novelty responses as a function of task demands and does not actually reflect the underlying mechanism by which the brain operates (Patryk, 2008). Given that in neurophysiological experiments animals are routinely trained to a criterion level, it is impossible to know what processes are occurring without experiments explicitly designed to test the effect of task acquisition.

7.2.3 Response decrements and LTD

Proponents of the response decrement theory of recognition memory contend that decrements may be driven by an LTD like process. Several studies have demonstrated that interfering with the molecular machinery mediating the expression of LTD produces deficits in recognition memory (Massey et al., 2008; Griffiths et al., 2008b). Critically however, given the numerous criticisms leveled at the response decrement theory, the data demonstrating a link between LTD and recognition memory require an alternative explanation.

A central tenet of this dissertation has been the need to understand neural processes from the perspective of networks rather than individual neurons. Operating from this perspective, it has been hypothesized that network storage capacity is dependent on the number of connections between neurons (MacGregor and Gerstein, 1991; Gawne and Richmond, 1993). For example, if networks of neurons are too connected an incoming stimulus may inadvertently lead to the excitation of neurons not previously involved in its representation thereby leading to noisy representations (i.e.

crosstalk). Moreover, this crosstalk would result in a decrease in the number of unique representations able to be stored in the network. One solution to this problem, similar to the tuning hypothesis, is that networks of neurons should act to reduce correlations between network members, thereby ensuring distinct representations at the neuronal level. To explore the implications of this view, activity of pairs of neurons was analyzed (**Chapter 5**). Critically these results (section **5.3.1**) demonstrate that there exists an experience-dependent decrease in the functional connectivity between neurons pairs in neurons in the rhinal cortex. Taken together with data demonstrating that blocking LTD interferes with recognition memory, these data indicate that (1) LTD may not be responsible for the observed response decrements and (2) LTD may act to disambiguate patterns of neural activity associated with different stimuli at the network level. Moreover, this view is consistent with data demonstrating that experience results in a rearrangement of the anatomical connectivity between neurons in PRC and TE (Yoshida et al., 2003).

7.2.4 Gamma oscillations

Gamma oscillations are a candidate mechanism by which the brain links together spatially distributed neurons. Moreover, this coordination of activity between neurons has been proposed as the solution by which the brain solves the binding problem (Singer, 1993; Gray, 1994; Tallon-Baudry and Bertrand, 1999). An extension of these hypotheses is that gamma oscillations should be elevated during stimulus encoding.

Previous studies in rodents and primates have largely supported these theories. However, most studies only demonstrate a linkage between spikes of single neurons and their phase preference relative to gamma. The data presented in **section 6.3.1** extend our understanding of the role gamma oscillations in coordinating the activity between neurons in the rhinal cortex by demonstrating that the power of gamma oscillations enhances the correlated activity between neurons. Moreover, the data in **6.3.2** demonstrate that gamma oscillations in the rhinal cortex are larger for novel stimuli (i.e., during encoding) than for familiar stimuli. These data support results from both humans and rodents regarding the role of gamma oscillations in the rhinal cortices.

Critically however, as discussed in **6.3** and **6.4**, we cannot compare our results to previous findings of gamma oscillations in the hippocampus of primates performing a very similar task (Jutras et al., 2009). This is primarily due to the fact that Jutras et.al., (2009) do not report whether there exists a difference between gamma oscillations for novel v.s. familiar images.

Finally, **6.2.2** showed that traditional methods of analyzing gamma oscillations can be heavily influenced by artifacts introduced by transients from action potentials contaminating the field potential signal. These data extend recent reports from Zanos et al., (2011) and Ray and Maunsell (2011) by demonstrating that spike contamination of the LFP is not a problem limited to the primary visual cortices.

7.3 Suggestions for future experiments

As with all studies, the present set of experiments raised more questions than it answered. Moreover, since the original inception of these experiments there has occurred a tremendous growth in the ideas and data surrounding the function of the medial temporal lobe. The synthesis of our observations along with new data from other laboratories suggests a series of future experiments

7.3.1 Perceptual similarity, encoding and tuning specificity

A number of studies have demonstrated that perirhinal cortex is crucial for the discrimination of highly similar visual scenes and objects (**Section 2.2.1**). However, recent evidence has demonstrated that animals with hippocampal lesions are similarly impaired in perceptual discrimination tasks. Critically however, there exist no electrophysiological data from behaving primates that examines how neurons in the PRC or Hippocampus are differentially engaged by highly similar objects.

7.3.2 Training induced response patterns

As discussed at the end of chapter 4, the prevalence of novelty responses in the literature could be due to animals receiving significant overtraining on a novelty discrimination task, perhaps even in the absence of the animal being required to make a behavioral response. This of course begs the question, can experimental design itself become a self-fulfilling prophecy? This experiment could be done within an animal by recording a large set of sessions in which the animal passively views stimuli and another

later set of sessions in which the animal is forced to make a decision regarding the familiarity/novelty of the stimulus.

7.3.3 Relating behavioral responses to tuning differences

The current data show that networks of neurons can undergo experience-dependent changes in their connectivity profile. The question becomes whether these changes are linked to observable changes in behavior. The primary prediction is that if network decorrelation improves the representation of a stimulus, then these changes should be linked to better discrimination performance by the animal. Moreover, it has been suggested, but not demonstrated, that highly similar stimuli may overlap in their representations at the neural level. Similarly, it may then be asked whether highly similar items are more correlated at the network level? In a similar vein, future studies should characterize the extent of the inter-stimulus variability to better understand the process.

7.3.4 Establishing the link between network tuning and LTD

LTD has been linked to recognition memory performance and the discussion in Chapter 5 suggested that LTD may be the mechanism driving the observed decreases in correlation strength between neurons. Future studies must establish whether these two phenomena are causally related. However, experiments of this type are not well suited for a primate model. Consequently, a similar task to ours would have to be developed for the rodent. The first step in this regard would be to establish whether rodents show

similar changes in functional connectivity for novel and familiar stimuli. Provided these findings generalize to rodents, future experiments would be faced with the difficulty of conducting simultaneous localized drug delivery and high-density multi-unit recordings; which are still relatively difficult to realize. An alternative route would be the generation of a line of transgenic rodents with subregion specific tetracycline inducible deficits in LTD. This approach would allow a more nuanced control of plasticity mechanisms at the molecular level.

7.3.5 Time course of network tuning

While exciting, the discovery of experience-dependent changes at the network level require further characterization to fully understand the implications of the phenomenon for the behaving animal. A fundamental question which must be answered is what is the time course of this tuning. *In vitro* LTD induction in cortex and hippocampus occurs rapidly following tetanic stimulation, however no data exist showing LTD induction in response to behavioral training. Whitlock et al. (2006), however, demonstrated that LTP and associated molecular markers are rapidly induced (~ 10 minutes) following training on a single trial of an inhibitory avoidance task. Experimentally, this question could be asked by using an extremely large stimulus set in which subgroups of stimuli are tested at different latencies, by analyzing groups of stimuli at different latencies, should reveal how quickly the phenomenon can be induced.

7.3.6 Dissociating the effects of object and place in the hippocampus

The data presented in Chapter 5 demonstrated that pairs of hippocampal neurons, in our task, show very little correlated activity. In contrast a study by Hori et al., (2011) showed very high levels of correlations between a large proportion of pairs of hippocampal neurons during real and virtual foraging tasks. This difference is not entirely surprising given that 2DG imaging studies of CA3 activity suggest that this region may not be engaged during simple memory tasks (Sybirska et al., 2000), potentially explaining the difference between Hori et al., (2011) and the present data. It is interesting to speculate whether the synchronous activity in hippocampal circuits is a requirement for episodic memory formation; effectively allowing features of an environment to become bound to the environment itself.

7.4 Conclusions

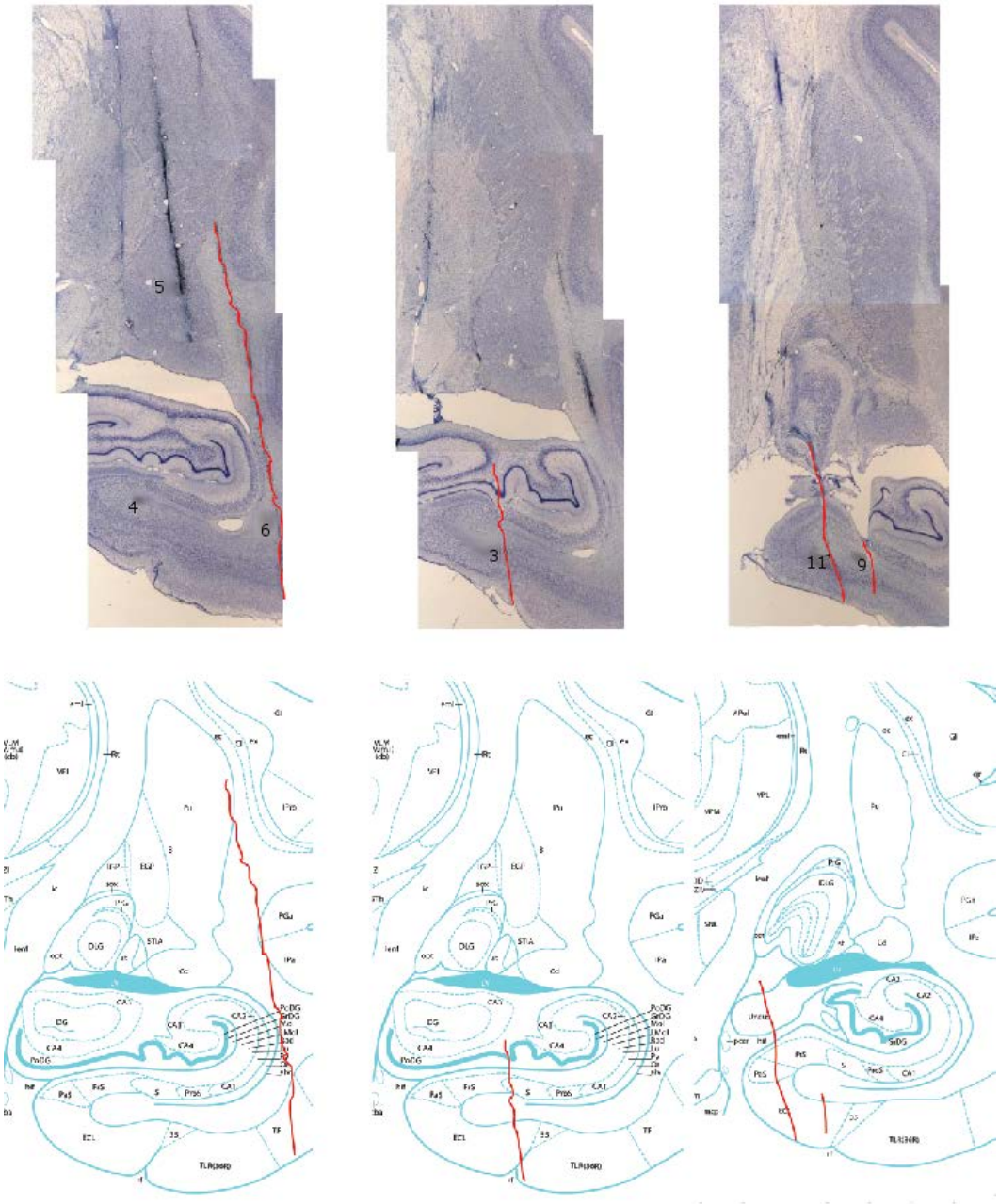
When I first began work on this dissertation, I had a fairly skeptical approach towards the idea that response decrements had anything to do with recognition memory. Instead, I hypothesized that perhaps the data were misunderstood and what had been previously interpreted as familiarity or novelty detection was more likely a result of tuning of neurons as stimuli became more familiar. As is often the case, the answer was not so simple. First, I found no neurons which exclusively increased or decreased their firing rates, even when a more liberal criterion was used. Secondly, and quite unexpectedly, I discovered a significant dissociation between regions showing tuning and those not showing tuning. Specifically, it appears that perirhinal and

hippocampal cortices, both higher level association regions, do not show experience-dependent tuning, while unimodal visual areas do. My new theory is that tuning in higher level association areas may be particularly detrimental to the encoding of information there, as these regions are tasked with building associations across modalities and that tuning here may inadvertently lead to the destruction of behaviorally relevant associations.

The question of storage constraints in the nervous system, however, extends beyond the activity of single neurons, and focused on the "wire together" component of Hebb's theorem. It had always struck me that the unintended consequences of this continual increase in synaptic strength would eventually saturate the connections in the nervous system. Decades of research have demonstrated that the nervous system compensates for the "wiring together" by a process of long term depression, in which the connections between neurons become weaker. However, whether and how such mechanisms occur in the primate was completely unknown. For a variety of reasons, many of the studies demonstrating LTP/LTD in rodents are not easily reproduced in primates, but those that do largely replicate the findings from rodents (Urban et al., 1996) . Faced with this constraint, required employing a set of analytical techniques to attempt to infer whether there exist differences in the functional connectivity between pairs of neurons. Surprisingly, a small, but significant, effect could be seen in the correlation strengths between neurons between novel and familiar images. These findings however are still only correlative. Linking these phenomena in the primate will

require a significant amount of technical insight and clever experimental design. It is my hope that in reading this dissertation, a future student may find inspiration and attempt to find the answers that, for now, continue to elude us.

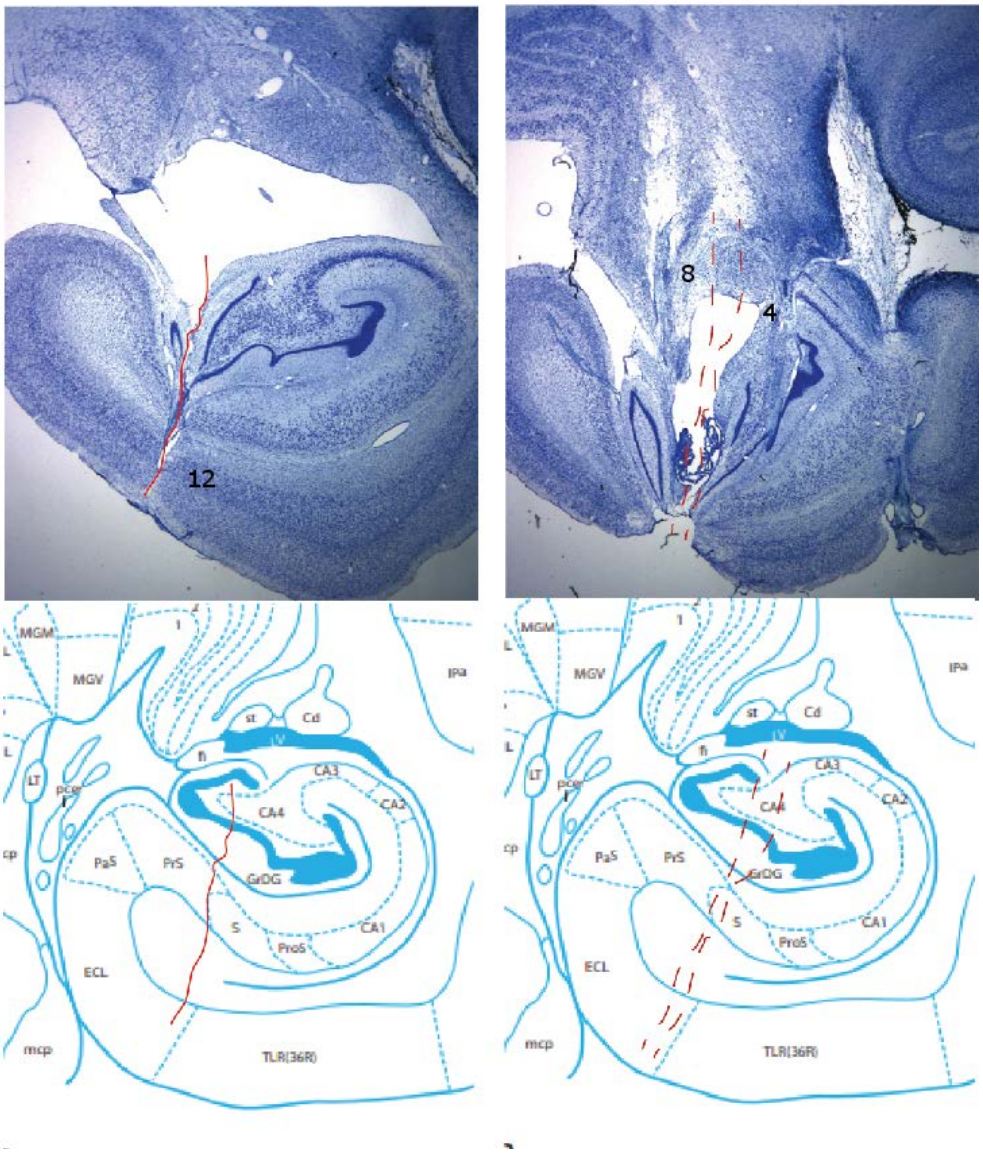
APPENDIX A – ELECTRODE TRACK RECONSTRUCTION



MMU25516 (Buzz)

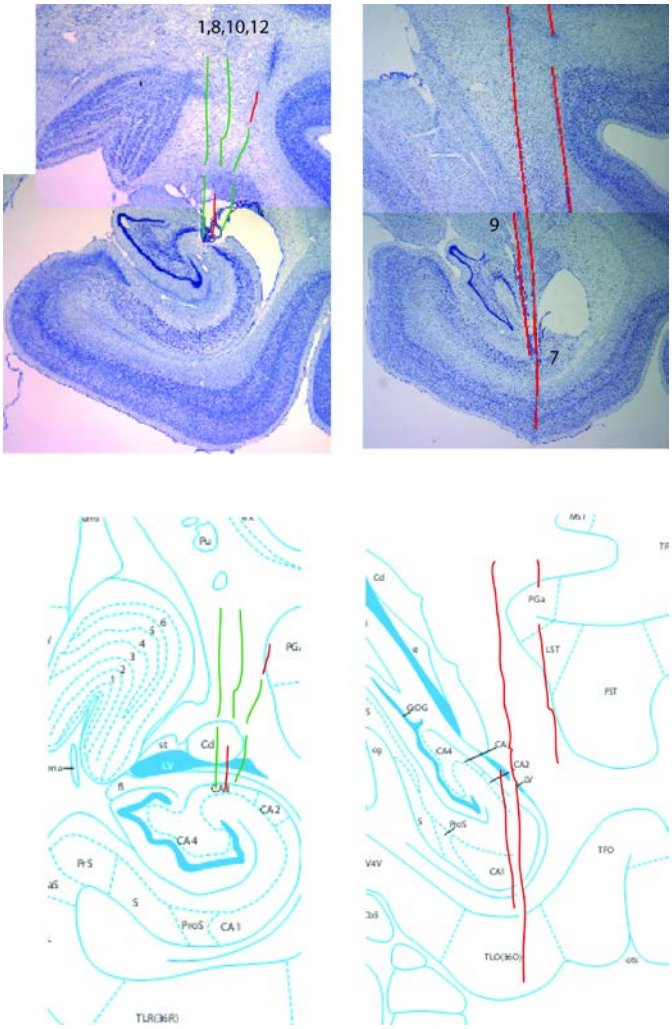
Single units were recorded on tetrodes 3, 6, 8, 9, 11. Histological identification of the record locations was very straight forward. TT3, passed first through CA3 and then

through TLR/36R. TT6 passed through area TF. Both TT9 and TT11 were located in the Entorhinal cortex.



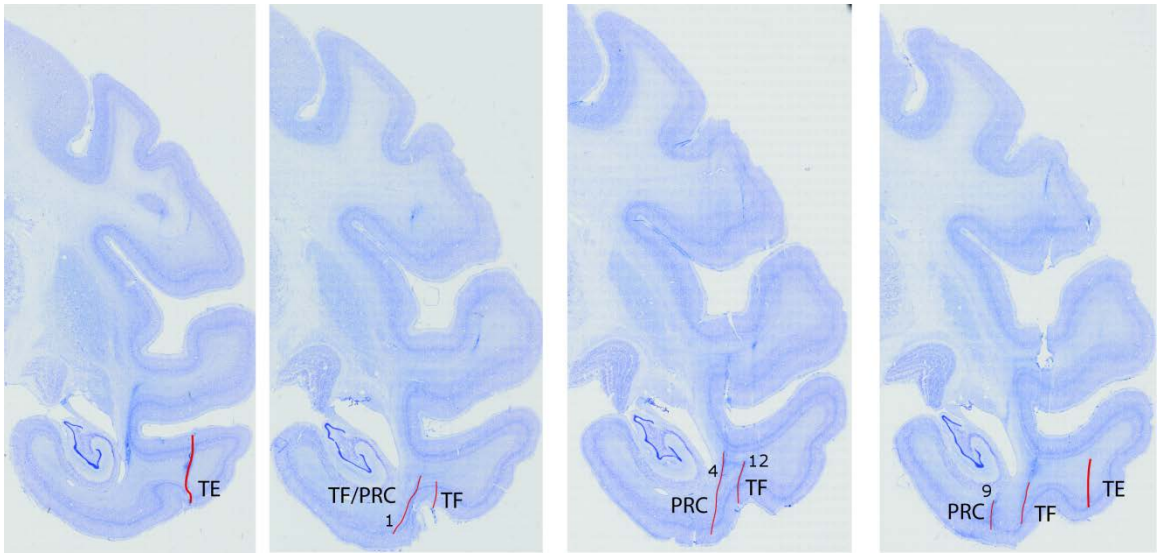
MMU24299 (Clea)

Tetrodes with single unit responses were 8, 4 and 12. However, due to a combination of damage caused by the implant, tissue processing artifact (tearing, shrinking, etc), as well as due to the time elapsed from the explant of the implant from the right side (VARNOV), locating individual electrode tracks was not possible, though it appears virtually all tetrodes passed through the entorhinal cortex.



MMU17298 (Nessim)

Single units were recorded on Tetrodes 1, 7, 8, 9, 10, 12. Reconstruction was difficult due to 1) the right side being implanted first,and 2) cutting angle of the sections not being perfectly perpendicular to the sections. Single unit responses and field potential recordings significantly improved the confidence of identifying tetrode position. Tetrodes 1, 8, 9, 10, 12 were all located in CA3, Tetrode 7 was located in the posterior PRC. Red lines-represent tracks visible on the current section, green lines indicate tracks on proximate slides. The reader will note that certain aspects of the histology do not correspond 1:1 with the atlas reference. For instance while the left section matches closely at the level of the thalamus and the hippocampus, the occipitotemporal sulcus is not yet present. Consequently, the atlas reference used is the one which most closely resembled the structures of interest.



MMU07119 (Joan)

The reconstruction from Joan suffers from similar problems as that of Nessim. Specifically, it appears that the thalamus is out of register with the location of the hippocampus because of tilt angle during sectioning. Moreover, there is at times a mismatch of the hippocampal level and surrounding cortical sulcii—as seen in the Paxinos Rhesus atlas. Consequently no reference image from Paxinos included. Rather, electrode tracks and regions have been marked on the digitized histology sections. Tetrodes 1, 4, 9 and passed through the PRC (35/36), while tetrode 12 passed through TF.

APPENDIX B – ANIMAL HISTORIES

This appendix provides a summary of the histories for each of the animals used in the current dissertation. Histories includes: Biographical information, prior projects and significant medical events.

Joan (MMU07119)

Joan was born on August 30, 1971, in an outdoor field cage at the California National Primate Research Center, in Davis, California, where she spent her young adult life, until she was removed on December 15th, 1995. Her mother, *born at CNPRC*, was of Indian origin. Her mother's CNPRC number was MMU01706; and the sire, also of Indian origin, was MMU00273.

Prior Projects:

1) Center Long Term Breeding Colony (CRB01) - to maintain the primate population at the Center;
2) Aged Rhesus Macaque Colony (OLD01)- that holds animals that may be used for aging projects
3) IcG Angiography and Histologic IcG Localized Age-related Macular Degeneration (CHG01)- where she was examined for the possibility of age related macular degeneration; which she did not have.
4) Behavior Studies of Aged Macaques (OLD04), Cognitive Function of Aged Macaques (CFM01) in which cognitive tests were given in a WGTA apparatus

5) Neurophysiology of Facial Perception (AMA04) where she was presented with pictures of other CNPRC primates making different facial expressions.

6) Mechanisms of Associative Memory Impairment in Aging – PROJECT AG18890 **–** grant to do cognitive testing in young and old monkeys and to trouble shoot chronic hyperdrive implant procedures.

7) Neurobehavioral Relations in Senescent Hippocampus AG003376. (BAR01) R01 that supports the experiments in the present thesis.

Joan's first electrophysiological data was obtained on 8/19/2002, and her last recording session was on 3/10/2003. From March 13 to April 03, 2003 Joan was retested on the delayed non-matching to sample task that she had received 5 years previously. The data collected during this retest was compared to her previous performance. Her performance was remarkably stable across this time period, which included two hyperdrive implants. Joan was euthanized on 02/16/07.

Medical History

Joan was housed indoors for approximately 8 months, and then was moved to a corncrib in the outdoor colony on April 26, 1972. She spent approximately 23 years in this colony and the following 10 years single caged in geriatric housing. She conceived 15 times from age 3.5 to age 21 and raised 13 infants. Her medical records indicate

that she had multiple minor traumas. Her first live birth was on April 26, 1977 and her Fifteenth and final pregnancy occurred on May 13, 1992.

Joan was taken to the University of California Imaging Center in Sacramento twice for magnetic resonance imaging data collection. The first was on March 16, 2001 to develop an atlas that allowed targeting of tetrode recording probes to her medial temporal lobe. The second procedure, on February 28, 2002, involved iv administration of gadolinium, allowing higher resolution images – enhanced contrast for analysis of cerebral blood volume.

Buzz (MMU 25516)

Buzz was born on April 30, 1990, in an outdoor field cage at the California National Primate Research Center, in Davis, California. He resided there for approximately 5 years before being shipped to the Southwest National Primate Research Center in San Antonio Texas. He was reacquired by the CRPC in 1995. He was removed from the outdoor colony on May 28th 1996. His mother, *born at CNPRC*, was of Indian origin. His mother's CNPRC number was MMU17203; and the sire, was unknown.

Prior Projects:

1) Center Long Term Breeding Colony (CRB01) - to maintain the primate population at the Center.
2) Neuroanatomical Studies if the Primate Limbic System (AMA02). Received primarily behavioral testing and blood draws. Was a sham surgical control (anesthesia only).
3) Transdermal Fentanyl in Rhesus Macaques (FEN02) – received an indwelling femoral catheter for use in fentanyl study.
4) Cardiodynamic Safety Study of CT50494 (COR02) – intravenous pharmacokinetic study of an experimental anticoagulant.

5) Determination of Serum Bile Acid Concentrations in Rhesus (DIC01) – received multiple blood draws.

Because of a terminal ear infection, Buzz was ill at the end of his recording session. Therefore he was not retested on the delayed non-matching to sample task, making it impossible to compare across years from the time of his initial testing. His first electrophysiological data was obtained on April 28, 2003, and his last recording session was obtained on July 21, 2003. Buzz was euthanized on 11/14/03.

Medical History

Buzz was housed outdoors for approximately 5 years, and then was moved to an indoor cage in *speed space* (a type of indoor housing). He spent approximately 5 years in speed space then was transferred to the animal wings. Buzz has no offspring. His medical records indicate that he had multiple minor traumas. Buzz was taken to the University of California Imaging Center in Sacramento twice for magnetic resonance imaging data collection. October 11, 2001 Buzz received a structural MRI to develop an atlas that allowed targeting of tetrode recording probes to his medial temporal lobe. On July 11, 2002 Buzz was taken to Sacramento for resting functional scan, MRI, which involved iv administration of gadolinium, allowing higher resolution images – enhanced contrast for analysis of cerebral blood volume. Buzz was taken for another MRI scan

which revealed that an inner ear infection resulting from trauma to the ear drum had progressed into his brain. He was euthanized on November 14, 2003.

Clea (MMU 24299)

Clea was born on May 16, 1988, in an outdoor field cage at the California National Primate Research Center, in Davis, California. She was removed from the outdoor field cage 4.5 years after birth (3/3/1993) and was singly housed until entering the BAR01 project. Her mother, born at CNPRC, was of Indian origin. Her mother's CNPRC number was MMU19780; and the sire was unknown.

Prior Projects:

1) NICHD Infants and Juveniles (REP10) – receives animals for possible use in experiments.
2) Center Research Pool(CRX01) – houses animals for use in experiments.
3) Iron Absorption From Infant Formula (LAC10) - Clea received a dose of infant formula which was radioleabled (1uCi Fe59 + 1 uci Fe55). She also received a whole body scan to assess iron absorption

4) Calcium Absorption From Human Milk And Infant Formula (LAC11) – Clea received a radiolabeled infant formula (.5 uCi Ca47), as well as a whole body scan to examine calcium absorption.
5) Environmental Enrichment-Lab Primates (FUN03) – A training and pairing house protocol.
6) Vaccination for HIV and AIDS (AID06) – Clea was immunized with HIV-1 gp120 (HIV envelope glycoprotein), and two subsequent blood draws.
7) Center Research Breeding Program (CRB01) - to maintain the primate population at the Center.
8) Maternal Allogenic Vaccinations (MAV01) – She was given a dose rhPBL in adjuvant 1x during pregnancy
9) Adult and Adolescent Response to Acute Ethanol Intoxication (GOL04) – Clea was a control animal in this study, given canola oil 3x.
10) Endocrine Disruption on Adolescence – Methoxychlor (GOL06) - dosed with DES, 0.5mg/kg NGT twice.
11) Macaque Sperm Cryopreservation (MEY01) – Given superovulation injections (FSH + Antide x 9 days)
12) Mechanisms of Associative Memory Impairment in Aging – PROJECT AG18890 – grant to do cognitive testing in young and old monkeys and to trouble shoot chronic hyperdrive implant procedures
13) Neurobehavioral Relations in Senescent Hippocampus AG003376.

(BAR01) R01 that supports the experiments in the present thesis

14) Estrogen and the Aging Brain: Animal Core (EST02) – was held for the project but not tested.

Clea was retested on the delayed non-matching to sample task starting on April 17th 2006 for 15 sessions. These data were compared to her performance approximately 4 years previously on the task. Importantly, her accuracy was not significantly different from her previous performance scores after all recordings had been made. Clea's first electrophysiological data was obtained on September 15, 2005, and her last recording session was obtained on April 14, 2006.

Medical History

Clea was born outdoors and spent approximately 4.5 years in the outdoor colony, then moved to indoor housing for approximately 14.5 years. She had four offspring; the first was born on May 14, 1992 her last born November 8, 1998.

Clea was taken to the University of California Imaging Center in Sacramento twice for magnetic resonance imaging data collection. October 11, 2001 Clea received a structural MRI to develop an atlas that allowed targeting of tetrode recording probes to his medial temporal lobe. On July 11, 2002 Clea was taken to Sacramento for resting functional scan, MRI, which involved iv administration of gadolinium, allowing higher

resolution images – enhanced contrast for analysis of cerebral blood volume. Clea was euthanized on 06/16/06.

Nessim (MMU 17298)

Nessim was born on June 17, 1977, at the California National Primate Research Center, in Davis, California; he was then transferred to the University of Texas System Cancer Center where he lived for 16 years. He was reacquired by the CNPRC at AGE 17. His mother, *born at CNPRC*, was of Indian origin. His mother's CNPRC number was MMU07061; and the sire, MMU08241 was acquired from Charles Rivers Research Primates Inc.

Prior Projects:

1) Aged Rhesus Macaque Colony (OLD01)- holds animals that are aging, and give routine health care

2) Center Non-Breeding Research (CNX01)

3) PCR Cloning of Novel Tyrosine Phosphatases from Rhesus (HVL05) – One time biopsy of fat, muscle, and ultrasound-guided liver biopsies.

4) Metabolic Effects of a Novel B-3 Adrenergic Agonist in MMU's (HVL04) – One time muscle biopsy.
5) Mechanisms of Associative Memory Impairment in Aging – PROJECT AG18890 – grant to do cognitive testing in young and old monkeys and to trouble shoot chronic hyperdrive implant procedures
6) Neurobehavioral Relations in Senescent Hippocampus AG003376. (BAR01) R01 that supports the experiments in the present thesis

Nessim was euthanized due to medical issues prior to completing retesting on the delayed non-matching to sample task. Consequently no data was available to compare across years from the time of his initial testing. Nessim's first electrophysiological data was obtained on March 26, 2006, and his last recording session was obtained on February 9, 2007.

Medical History

Nessim spent approximately 18 years in the outdoor colony and 12 years in indoor housing, he has no offspring born at CNRPC. His medical records indicate that he had multiple minor traumas.

Nessim was taken to the University of California Imaging Center in Sacramento twice for magnetic resonance imaging data collection. October 11, 2001 Buzz received a structural MRI to develop an atlas that allowed targeting of tetrode recording probes to

his medial temporal lobe. On July 11, 2002 Nessim was taken to Sacramento for resting functional scan, MRI, which involved iv administration of gadolinium, allowing higher resolution images – enhanced contrast for analysis of cerebral blood volume. He was euthanized on February 16, 2007.

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