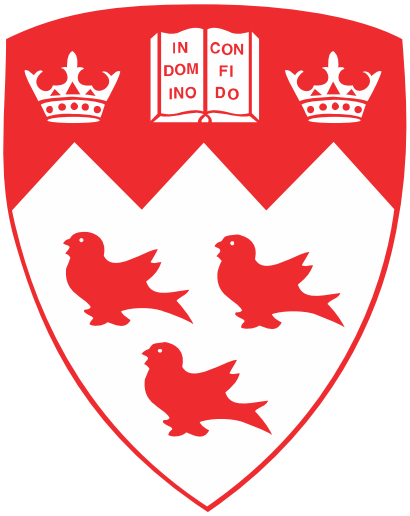
HIPPOCAMPAL FUNCTION IN NON-HUMAN PRIMATES



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For Mom, Liberata & Dad, Giuseppe;

Every moment working on this has merely been a reflection the values you've instilled in me.

I'll never be as smart, hard-working, or wise as you; but every day, I'll try.

ABSTRACT

The hippocampus is a phylogenetically ancient brain structure that has been shown to be critical for spatial navigation and memory. Decades of research have uncovered neurophysiological correlates of each function in the activity of hippocampal neurons, but debate continues over the primacy of each one. This debate exists, at least in part, because navigational and non-spatial mnemonic signals are difficult to simultaneously observe and disentangle with contemporary techniques. To address this, this thesis details the development of a novel experimental paradigm that combines virtual reality tasks with hippocampal neurophysiology in monkeys (*Macaca mulatta*). Single neurons in the right mid/posterior hippocampus were recorded while subjects completed a foraging task and an associative memory task in the same virtual environment. Using multiple analytical techniques, it was shown that hippocampal neurons do encode information about space in each task. However, the code for space does not generalize across tasks. This can be attributed to encoding of trial-specific features of associative memory that vary depending on position in the virtual environment. Furthermore, it is not only the objects that are relevant to associative memory that are encoded by these neurons when the monkey is looking at them. A subset of neurons is activated by each object in the environment, and these representations change as a function of behaviour. Together, the work presented in this thesis shows that some, but not all predictions of spatial and mnemonic theories of hippocampal function are corroborated in monkeys completing tasks in a virtual environment. The points of divergence from established dogmas may have important implications for neuropsychological and computational theories of hippocampal function across species.

RÉSUMÉ

L'hippocampe est une structure cérébrale phylogénétiquement ancienne qui s'est avérée essentielle à la navigation spatiale et à la mémoire. Des décennies de recherche ont mis en évidence des corrélations neurophysiologiques entre l'activité des neurones hippocampiques et chacune de ces fonctions, mais le débat perdure sur la primauté de chacune. Ce débat existe, au moins en partie, car les signaux navigationnels et mnémoniques non-spatiaux sont difficiles à simultanément observer et démêler, à l'aide des techniques contemporaines. Pour y remédier, cette thèse détaille le développement d'un nouveau paradigme expérimental, combinant des tâches de réalité virtuelle avec la neurophysiologie de l'hippocampe chez le singe (*Macaca mulatta*). Des neurones individuels, de l'hippocampe moyen / postérieur droit, ont été enregistrés pendant que les sujets effectuaient une tâche de recherche et une tâche de mémoire associative, et ce dans le même environnement virtuel. En utilisant plusieurs techniques analytiques, il a été montré que les neurones hippocampiques encodent des informations sur l'espace dans chaque tâche. Cependant, le code de l'espace ne se généralise pas entre les tâches. Cela peut être attribué à l'encodage de caractéristiques spécifiques à la fonction de mémoire associative de chaque essai, qui varient en fonction de la position dans l'environnement virtuel. De plus, ce ne sont pas seulement les objets pertinents pour la mémoire associative qui sont encodés par ces neurones lorsque le singe les regarde. Un sous-ensemble de neurones est activé par chaque objet dans l'environnement et ces représentations changent en fonction du comportement. Collectivement, les travaux présentés dans cette thèse montrent que seulement certaines prédictions des théories spatiales et mnémoniques de la fonction hippocampique sont corroborées par des singes qui accomplissent des tâches dans un environnement virtuel. Les points de divergence à partir des dogmes établis peuvent avoir des implications importantes pour les théories neuropsychologiques et computationnelles de la fonction hippocampique chez les espèces.

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LIST OF ABBREVIATIONS AND ACRONYMS

WGTA	Wisconsin General Testing Apparatus
MS	Match-to-sample
NMS	Non-match-to-sample
DMS	Delayed-match-to-sample
DNMS	Delayed-non-match-to-sample
DR	Delayed response
DA	Delayed alternation

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Corrigan, B. W., **Gulli, R. A.**, Doucet, G. & Martinez-Trujillo, J. C. Characterizing eye movement behaviors and kinematics of non-human primates during virtual navigation tasks. *J Vis* **17,** 15–15 (2017).

Doucet, G., **Gulli, R. A.** & Martinez-Trujillo, J. C. Cross-species 3D virtual reality toolbox for visual and cognitive experiments. *J. Neurosci. Methods* **266,** 84–93 (2016).

CONTRIBUTION OF AUTHORS

For all experiments included in this thesis, RAG designed the experiments, virtual environments, collected and analysed data, and wrote the present monograph. Lyndon R Duong contributed to data analysis. Benjamin W Corrigan contributed to data collection and eye movement parsing, writing and editing. Guillaume Doucet contributed to virtual environment design and data pre-processing. Sylvain Williams contributed to experimental design. Stefano Fusi contributed to data analysis and writing. Julio Martinez-Trujillo contributed to experimental design, writing and editing. Matthew L Leavitt, Jesse Jackson, and Ramon Nogueira offered critical input and discussion throughout.

PROLOGUE

"The patient is a 70-year old right handed man who presented to the emergency room with a chief complaint of 'I got lost on my way here'. The present illness began on the same day shortly after awakening. The patient noted the sudden onset of vertigo and unsteady gait. He denied any weakness but decided to come to the ER of our institution for evaluation. The patient is retired and had worked in this Hospital as a psychologist for 20 years and drove the same route every day. While driving his car he suddenly found himself on a back road. Although he knew where he was he could not figure the way out. After driving aimlessly for 20 min the patient decided to call a friend and asked him for help. A friend finally drove him to the hospital."

The hippocampus is a striking area of the mammalian brain; it is the phylogenetically oldest area of our cortex, with a conspicuous anatomical structure that has captured the interest and ire of anatomists, naturalists, physicians, physiologists, and neuroscientists for centuries. Its anatomical structure is instantly recognizable, and has not markedly diverged across species for millions of years. Our understanding of hippocampal function, in contrast, has evolved at an incredible pace over the last two centuries, generating theories that show all the hallmarks of natural selection and common descent. The quote on the previous page is from a case study in which a patient presented with a right posterior hippocampal stroke (Aradillas et al., 2011): what are the fundamental functions of the hippocampus that were perturbed to produce this patient's deficit?

The contemporary understanding of the hippocampus is that this region receives highly processed information from all sensory modalities, and that this information is processed to subserve two cognitive functions: memory and spatial navigation (Schiller et al., 2015). Some offer compelling theories suggesting the primacy of spatial information in the mammalian hippocampus; furthermore, that this network has been co-opted through evolution to subserve memory by providing a spatial context for objects and events to be anchored through time (Buzsáki and Moser, 2013). This theory is driven forward by a wealth of literature in rodents completing tasks that require spatial navigation (see, e.g. (Moser et al., 2017)). Non-mammalian homologues of the hippocampus have been proposed after determining where brain lesions produce the most significant perturbations on spatial navigation tasks (Murray et al., 2017). An alternative theory argues that the primary function of the hippocampus is memory, with information related to space, time and sensory percepts being bound as conjunctive representations in neural ensembles in the hippocampus (Eichenbaum, 2017a). This theory is substantiated by a vast literature on hippocampal function in humans, which has been concisely reviewed with focus on developmental amnesia (Elward and Vargha-Khadem, 2018), and cognitive functions that are perturbed (Maguire et al., 2016) and preserved (I. A. Clark and Maguire, 2016) in patients with bilateral hippocampal lesions. Proponents of either theory have deemed each the evolutionarily distal *raison d'etre* of the hippocampus. Though this debate over primacy continues, most researchers would agree that substantial evidence points to hippocampal involvement in both memory and spatial navigation.

Studies that directly examine hippocampal encoding of spatial maps and mnemonic processes like those affected in lesion patients are scarce for several reasons. First, a large

methodological gap exists between studies of spatial mapping in rodents and discrete tests of memory performance in humans (Buzsáki and Moser, 2013; Eichenbaum and N. J. Cohen, 2014; Ekstrom and Ranganath, 2017; Schiller et al., 2015). Second, diverse behavioural repertoires across species based on the structural organization of sensory systems and corresponding reorganization of sensory inputs to the hippocampus make cross-species comparisons of activity amongst hippocampal neurons complex (Murray et al., 2017; Preuss, 2000). Non-human primates provide unique advantages as a model species to study the nexus of spatial and mnemonic hippocampal function simultaneously. Non-human primates are capable of complex non-spatial associative learning, and share a high degree of brain homology with humans. Though electrophysiological recordings from the non-human primate hippocampus are extremely rare relative to rodents, recent advances in surgical neuronavigation have made it possible to target hippocampal recording sites with extremely high fidelity. Innovation in virtual reality platforms has allowed for the development of new paradigms to dissociate spatial and non-spatial response profiles in single neurons.

In this monograph, I present the results of a years-long effort to add some experimental data to the gap between spatial and non-spatial theories of hippocampal function in non-human primates. **Chapter 1: Literature Review** provides a fuller account of the contribution of non-human primates to our current understanding of hippocampal function than currently exists in the literature; along the way, space is given for nuance and context that are often lost while distilling literature, in hope that some of this bears relevance today. In **Chapter 2: General Methodology**, the aspects of the methodology relevant to all experiments are described, much of which was novel and/or custom-built for this experiment. **Chapter 3: Spatial Information in the Hippocampus** shows the results of a direct comparison of spatial encoding in the non-human primate across cognitive tasks that take place in the same virtual environment. In **Chapter 4: Non-spatial Information in the Hippocampus**, neural correlates of behaviour are identified that may account for differences in spatial encoding across tasks. In **Chapter 5: Representation of Foveated Objects and Changes with Learning**, neuronal activity is examined at a much finer resolution — within individual foveations — with the goal of characterizing changes in firing rate and learning at a resolution not afforded by other research paradigms. Finally, in **Chapter 6: Discussion**, novel results are integrated into the context of previous literature, with the hopes of guiding the reader towards new ideas.

1 LITERATURE REVIEW

"Strange thing about learning; the farther I go the more I see that I never knew even existed. A short while ago I foolishly thought I could learn everything - all the knowledge in the world. Now I hope only to know of its existence, and to understand one grain of it."

Daniel Keyes, Flowers for Algernon, pg 153

1.1 Historical context for the study of hippocampal function in non-human primates

There is a commonly-told narrative of research exploring hippocampal function in primates (R. E. Clark, 2018; Squire, 1992; Suzuki, 2008). This narrative begins with the striking and famous epilepsy patient HM. His "very grave recent memory loss" after bilateral resection of temporal lobe structures was publicly presented by William Beecher Scoville in 1953, and more thoroughly described years later with Brenda Milner. In this publication, it was proposed that damage to the hippocampal formation specifically resulted in HM's specific memory disturbances (Scoville and Milner, 1957). This striking case inspired a search for an animal model of memory; non-human primates were assumed to be ideal for this, given their ability to learn complex concepts and similar gross brain anatomy to humans. However, years of attempts to reproduce amnesic-like memory deficits search were largely fruitless, even when led by Milner and other scholars of the temporal lobe system (Orbach et al., 1960). Much was made of these negative reports, and the functional homology of the hippocampus across primate species was questioned. Decades later, lesion work showed some homology between monkey models of amnesia and the clinically described deficits in patients like HM (Mishkin, 1978), and spatial configuration may be a critical part in uncovering these deficits (Gaffan, 1994). Unlike rodents, where place cells fire action potentials when animals occupy a specific part of a familiar environment, homologous cells in the primate hippocampus are selective for particular spatial views and gaze position within the environment (Rolls, 1999). Qualitatively similar activity can be observed from hippocampal neurons in the human temporal lobe during virtual navigation (Ekstrom et al., 2003). As of the time of writing, these publications spanning 1957-2003 have amassed over 6,000 citations. This narrative though is a narrow view of a larger literature, deep with nuance and discord. This chapter aims to more closely trace a narrative arc of hippocampal research involving non-human primates, to provide an appropriate context for the experiments conducted.

1.1.1 Hippocampal research prior to the 1930s

First described anatomically and named by Julius Caesar Arantius in 1587, the hippocampus was a perplexing brain structure from its discovery (Lewis, 1923). At the start of the 19th century, little was known and less was agreed upon about the mammalian hippocampus. Between 1816 and 1821, German anatomist Gottfried Reinhold Treviranus described the hippocampal connections with a variety of areas of the brain, stating "the

hippocampi are more than a mere convolution: no other convolution is connected, in such intimacy, with the totality of both the internal and external regions of the brain." He noted that the size of the hippocampus roughly correlates with the olfactory nerve across species. Together, these points suggested a possible involvement in memory and olfaction, since memory relies on rich inputs and is strongly evoked by odours (translated by (Meyer, 1971), pg. 87). Between 1876 and 1878, Meynert and other comparative anatomists had also noted that coloration of the hippocampus was distinct from the rest of the cerebrum, closer to the white fibers of the olfactory lobe (Dodds, 1878). This same year, Broca published an authoritative examination of the organization of gross brain anatomy across mammalian species and coined the term "great limbic lobe" (see translation, (Broca, 2015)). Comparisons of the primate brain to non-primates constituted nearly a third of the work's volume, and Broca made the still-controversial claim that the gross hallmarks of brain anatomy were present in all mammalian species. The hippocampus was deemed a critical component of the great limbic lobe, and again associated with the olfactory function across mammals.

The function of brain areas was largely inferred based on structure until Ferrier reported his first results on the effects of experimental brain lesions and stimulations on behaviour (Ferrier, 1886). After performing temporal lobe lesions in non-human primates, he states that "the affections of smell and taste are evidently related to lesions of the hippocampal lobule and the neighbouring regions. The facts of comparative anatomy and the phenomena of electrical irritation [that evokes facial responses similar to those seen when monkeys are exposed to particularly offensive odours] show beyond all doubt that the hippocampal lobule is the centre specially related to the sense of smell." (pg. 320).

This conclusion was directly refuted by Brown & Schäfer in 1887 (publicly) and 1888 (in print; (S. Brown and Schäfer, 1888)). This study reports that in many monkeys with a variety of temporal lobe disturbances, no impairments of the sensory faculties were observed (unlike Ferrier), but a marked impairment and cognition and memory. In their experiments, they even had Ferrier visit to assess their monkeys directly; in only one case did Ferrier argue that some evidence for olfactory deficits could be seen. Brown & Schäfer refuted this observation. It was proposed that this may be due not only to local disturbances of the cortex, but disturbances to the vascular that feeds the cortex around the area of the lesion as well. In the following decades, these results would be interpreted in a vast number of directions; perhaps most notably, by Klüver and Bucy for support of their integrated theory of emotional regulation by temporal lobe structures.

Between 1887-1890, Korsakoff described patients with amnesia for recent events and other peculiarities of memory that he termed *cerebropathia psychica toxaemica*. Though memory perturbations were mentioned by many physicians preceding Korsakoff, he uniquely linked the mental state of these patients to peripheral neuropathy, which was eventually coined Korsakoff's Syndrome. The physical cause of Korsakoff's Syndrome was not definitively known, though there was evidence linking similar diseases to deterioration of the mammillary bodies, midbrain, thalamic nuclei, and cortex more generally. All of these areas would gain significance with regards to memory function through primate hippocampal lesion work in the 20th century.

In 1896, Kölliker applied the term "rhinencephalon" to cortical structures with a white surface, which included the olfactory lobe, hippocampus and septal region (see (Pribram and Kruger, 1954)). This term, or it's literal translation "olfactory brain" permeate the hippocampal literature through the mid-20th century, long after the olfactory view of hippocampal function was abandoned.

One of the first and most distinct clinical cases of memory impairment as a result of hippocampal complication was presented by Vladimir Bekhterev (or Wladimir von Bechterew), a Russian physician who authored over 800 papers. In 1900, he presented a post-mortem case of a 60-year-old man with a history of memory problems, fabrication and apathy. Upon dissection of the brain, a bilateral "softening" of the hippocampal gyri was noted, without sensory deficits alluded to in Ferrier's previous work (Bechterew, 1900). It is notable that in the following decades, physicians made attempts to categorize these patients' amnesiac fabrications. In one of these attempts, cases were described where patients recalled true events, but incorrectly placed them in space and time (Moll, 1915).

In summary, much of what was supposed of hippocampal function early in the 19th century and early 20th century was drawn from comparative anatomical studies of the brain. The prevailing view during this time was that the hippocampus was largely an extension of the olfactory system, and occasionally implicated in other primary sensory function. Later in the century, lesion studies in monkeys and clinical cases of hippocampal perturbation suggested specific forms of idiocy that could reflect memory deficits, and this work was referenced in cases of memory-related impairments in patients with damage to the hippocampus and surrounding cortex.

1.1.2 The 1930s-1950s

In 1937, James Papez expanded considerably upon Broca's work on the great limbic lobe, proposing a circuit for the regulation of emotion. In this work, Papez admits that the central function of the hippocampus has been unknown for centuries, but primarily considers it association cortex, where olfactory information meets "ideomotor" processes of the brain. With regards to its place in a circuit, Papez writes "Incitations of cortical origin would pass first to the hippocampal formation and then down by way of the fornix to the mamillary body. From this they would pass upward through the mamillothalamic tract, or the fasciculus of Vicq d'Azyr, to the anterior nuclei of the thalamus and thence by the medial thalamocortical radiation (in the cingulum) to the cortex of the gyrus cinguli." The relation of this circuit to emotional regulation led researchers to report monkeys' disposition after hippocampal lesion for decades to follow; much of the architecture of this circuit would not be linked to episodic memory deficits in Korsakoff's Syndrome until three decades later (Delay and Brion, 1969).

Heinrich Klüver & Paul Bucy tested Papez's model, shifting hippocampal research in a new direction. Klüver and Bucy first observed that a single rhesus monkey lacked anger or fear responses and investigated all objects -- animate and inanimate -- by placing them in their mouth following a bilateral temporal lobectomy (Klüver and Bucy, 1937). This animal did not seem to be able to recognize objects by sight, but only by touch, reminiscent of a form of "psychic blindness" originally described in the 1800s. Next, these authors elaborated to define psychic blindness as a loss of "the ability to recognize and detect the meaning of objects on the basis of optical criteria alone" (pg. 38) (Klüver and Bucy, 1938). They describe visual agnosia, oral tendencies, and emotional changes which were frequently reported on but seldom corroborated in hippocampal lesion studies for decades after. In the last of this trilogy of reports, they repeated their previous observations in additional monkeys that had been chosen specifically for their aggressive nature (Klüver and Bucy, 1939). Klüver and Bucy cite their work as evidence in favour of the hippocampus in emotional regulation rather than memory or sensory processing *per se*.

Dr Wilder Penfield carried out some of the most consequential work towards understanding hippocampal function in the 1930s. He understood and extended upon the ideas of Hughlings Jackson, who noted convulsions could be preceded by specific sensory auras or motor movements in 1867. To try to localize the epileptogenic brain tissue for excition, Penfield developed a direct electrical stimulation technique to reproduce the pre-

convulsive auras. Penfield noted that epileptic seizures were often preceded by "psychical auras", and stimulated temporal cortex in an attempt to reproduce these sensations in his patients. In 1938 Penfield noted for the first time that stimulation of the temporal lobe could produce a "psychical" state: an experiential hallucination or interpretive illusion (Penfield, 1958a; 1958b). Because of these observations, Penfield termed the temporal lobe "interpretive cortex". This term is curiously absent in modern literature; the sensations reported by Penfield's patients could not be assessed in non-human primates, but Penfield's model unquestionably informed future interpretations of deficits in hippocampectomized patients and experimental hippocampal lesions in the following decades.

Experimental work, particularly that of an exploratory nature in non-human primate temporal lobe slowed considerably during the war (see Pribram, Milner, or Maclean in (Squire, 1998) for first-hand accounts). Notably, a well-read, thorough and damning review marked a period of decline for the olfactory theory of hippocampal function in the post-war years (Brodal, 1947).

1.1.3 The 1950s

1.1.3.1 Lesion studies in the 1950s

Entering the 1950s, our understanding of cortex was very different than the current view; both in its structure and function. The behaviourism that dominated previous decades was beginning to yield to the cognitive revolution, and systematic experimental lesions became more common. This shift resonates through generations of scientific studies on hippocampal function in primates. There was a critical mass of investigators interested in studying the cognitive effects of localized lesions to many brain regions in non-human primates that were critical of mass action and equipotentiality. In a typical study of this time, a variety of lesions were conducted across a wide swath of cortex; afterwards, a wide variety of behavioural tests were conducted using variants of the Wisconsin General Testing Apparatus (WGTA) developed by Harlow & Bromer (Harlow and Bromer, 1938). These typically included spatial, visual and somesthetic discrimination tasks, alternation tasks, and delayed reaction tasks. If tests were only administered after cortical lesion, experimenters claimed that animals' learning faculties were being assessed. Sometimes tests were re-administered weeks after learning, or prior to cortical lesion; in these cases, the faculties of retention were assessed. Task structure during this time was highly variable, and results were

reported in tables and described qualitatively, making interpretation of effects inconsistent between research groups.

At Yale, neurosurgeon Karl Pribram set up a program to study the effects of different types of brain lesion on a wide variety of behaviours, launching a series of studies that would span decades. In 1950, behavioural deficits were described in one monkey with only temporal lobe damage (Blum et al., 1950). All areas of cortex were removed anterior to the vein of Labbé, except the posterior hippocampus, and a wide variety of sensory and perceptual tasks were done. This monkey was shown to be impaired in some discrimination problems, as well as conditional reaction and delayed reaction tasks. The authors claimed that this paper shows a complete failure to relearn a delayed-response problem in the monkey with temporal lobe ablation.

A promising graduate student at McGill University was sent to conduct experiments for his thesis work on localization of function with Pribram at Yale: this marked the start Mortimer Mishkin's prolific and influential career examining the effect of localized brain lesions on behaviour in non-human primates. Mishkin's thesis work included several studies of behavioural deficits following cortical and subcortical lesions in monkeys and baboons (Mishkin, 1951). The first published work of this collaboration suggested that the ventral temporal lobe and hippocampus specifically contributed to visual discrimination tasks, as opposed to the temporal pole, amygdaloid complex, or lateral temporal lobe (**Figure 1.1**; (Mishkin and Pribram, 1954). These results were corroborated in a second study, which also suggested that lesions to the hippocampus or amygdala alone had no deleterious effects on delayed responses or visual discrimination (**Figure 1.2**; (Mishkin, 1954).

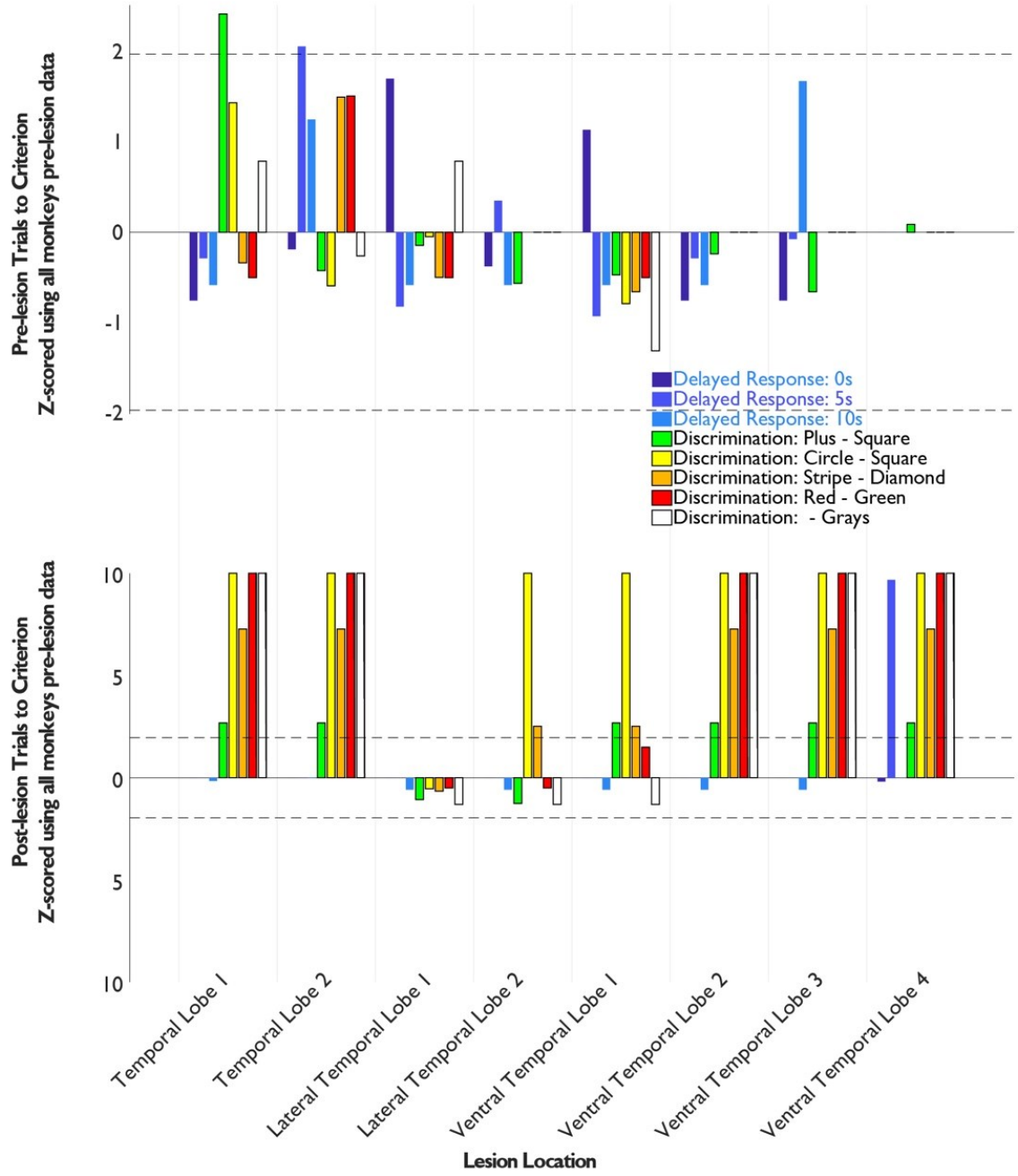


Figure 1.1. Results from Mishkin & Pribram, 1954

The number of trials to criterion (TTC) on eight tasks following varied lesions in 8 monkeys. Data was extracted from tables from (Mishkin and Pribram, 1954) and is shown graphically here for clarity. All bars are z-scored within each task, using data from all monkeys collected prior to experimental lesions. Dashed lines denote 1.96 standard deviations from the mean number of TTC for each task.

Top: Pre-surgical TTC for each monkey.

Bottom: Post-surgical TTC for each monkey.

These results show that many temporal ablations, especially those that include the ventral aspect of the temporal lobe, lead to discrimination deficits.

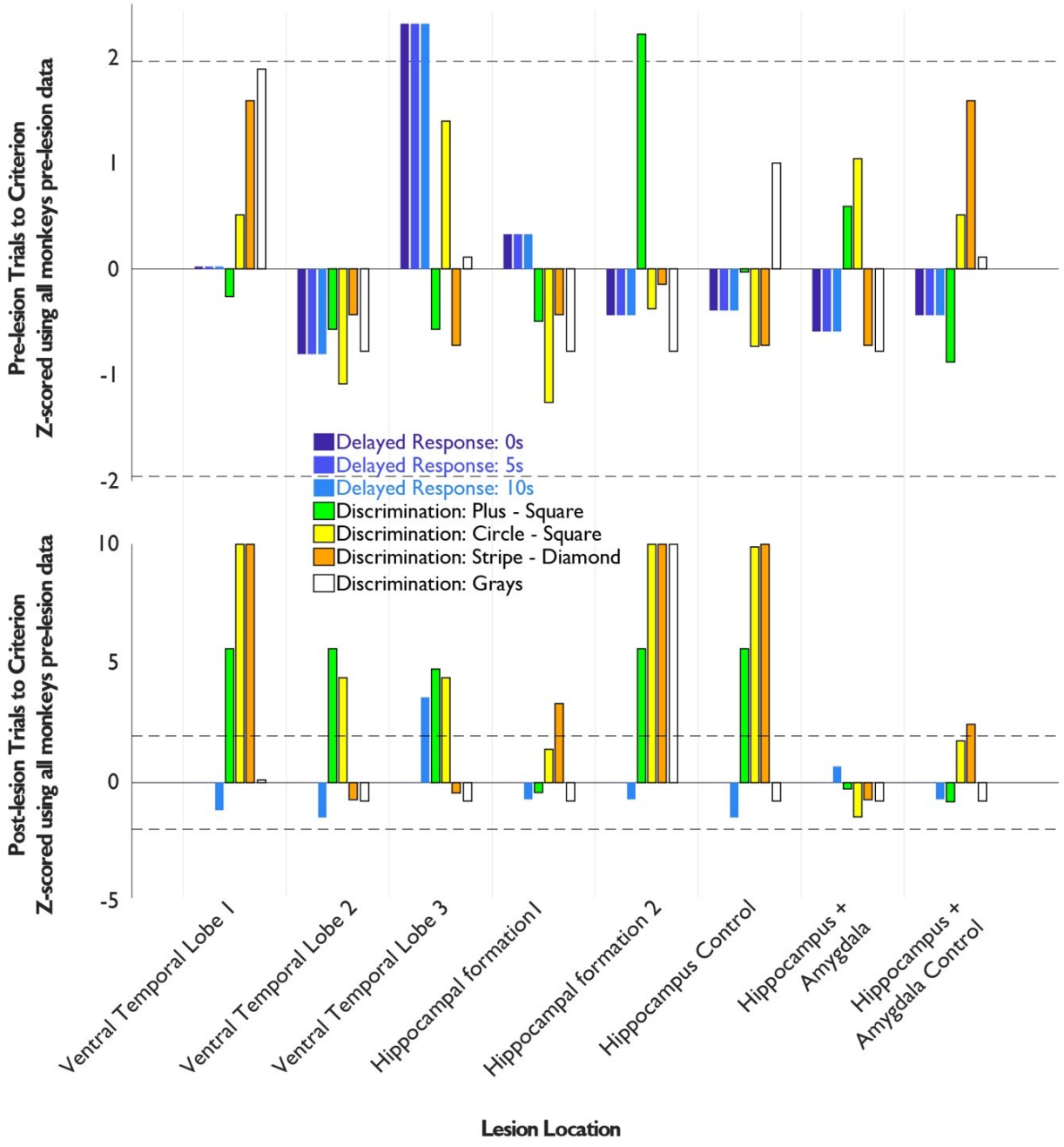


Figure 1.2. Results from Mishkin 1954

Experimental lesion data from 8 monkeys extracted from (Mishkin, 1954) and shown graphically. Conventions as in **Figure 1.1**. Though not consistent, some temporal lobe ablations affect performance on visual discrimination tasks, but not delayed response.

1.1.3.2 Electrophysiological and clinical studies in the 1950s

The first hippocampal recordings in non-human primates were published in 1954, alongside recordings from rabbits and cats (Green and Arduini, 1954). Across species, the hippocampal and neocortical record appeared desynchronized, though in monkeys, theta rhythm could not be evoked with odours, food, or social interaction. Hippocampal potentials were strongly affected by septal stimulation.

In the mid-1950s, a seminal series of papers was published that described impairments in "recent memory" and anterograde amnesia after bilateral hippocampal damage in patient HM and other clinical cases (Glees and Griffith, 1952; Milner and Penfield, 1955; Penfield and Milner, 1958). By 1959, Dr Scoville had started an intensive program trying to explicitly reproduce the temporal lobe ablations he carried out in HM on non-human primates. Over the ensuing decades, he would perform temporal lobectomies on hundreds of animals in pursuit of a model of HM's deficits (Scoville and Correll, 1973).

1.1.4 The 1960s

1.1.4.1 Notable lesion studies in the 1960s

In the 1960s, the landscape of proposed hippocampal functions vastly expanded, since 1) inconsistencies from previous studies with low sample sizes and variable lesion location/efficacy were interpreted in different ways, and 2) the number of task variants used increased dramatically (see also (Buzsáki, 2006), pg. 20). By my best estimation, 13 independent studies were published in the 1960s that involved lesions to the non-human primate hippocampus and some battery of cognitive tests. *Discrimination tasks* were used to assess the ability of monkeys to discriminate stimuli in sensory, tactile and auditory modalities. These included match-to-sample (MS) and non-match-to-sample (NMS) tasks. *Memory tasks* introduced delay periods with or without intervening distractors, such as delayed-match-to-sample (DMS; often used interchangeably with delayed response) tasks, and delayed-non-match-to-sample (DNMS) tasks. Delayed response (DR) and delayed alternation (DA) tasks are similar to DMS and DNMS tasks, respectively, though the cue and test stimuli are typically distinct in DR and DA tasks. One further variation should be noted; in some tasks, the behavioural response cannot be determined based on the cue stimulus alone; rather the subject must keep first cue stimulus in mind during the delay period, and the cue and test stimulus combination determines the appropriate behavioural response. These tasks have many names in the literature; stimulus-stimulus association tasks, context-

dependent tasks, conditional paired associate tasks. The effects of hippocampal lesions conducted in non-human primates from this this point forward should be used to fill a volume unto itself. A complete bibliography of these studies can be found in **Appendices I**; with limited time and space here, only a notable subset of this literature is discussed in detail.

This decade started with a highly influential attempt to replicate HM's deficits including experimental brain lesions in monkeys at McGill (Orbach et al., 1960). These authors claimed that previous work, such as Mishkin's 1954 studies included only moderate hippocampal resection, compared to those which induce memory loss in clinical patients. Furthermore, since the scientific community could not clearly describe the extent of HM's temporal lobe resection, a non-human primate model of recent memory loss without effects on attention, concentration, or reasoning was sought. Data from 13 monkeys was analyzed; since the lesion locations and behavioural tests across monkeys were not standardized, these results are difficult to interpret (see **Figure 1.3** for plotted results). Post-operative tests of visual object discrimination and post-operative learning were particularly important, since these tasks were specifically designed to mimic HM's deficits. Firstly, trials were interposed amongst the visual pattern discriminations as distractions, and secondly HM could not remember discriminations learned after his surgery, showing his impairment in recent memory. Because there was not a marked deficit on these tasks in the monkeys with combined amygdala and hippocampal lesions, it was concluded that the nature of the deficits in these monkeys were different than those in humans with allocortical damage. One proposed implication of these results was profoundly consequential, and has been cited as a prevailing view amongst the research community at this time: that species differences in organization of the affected brain areas preclude animal models from adequately replicating the amnesic syndrome.

In another study from McGill University co-authored by Rasmussen, monkeys were trained on two versions of a DMS task in auditory or visual modalities (Stepien et al., 1960). In a remarkably consistent result, monkeys with amygdalohippocampal lesions could not perform tasks in which they are required to keep the identity of a stimulus in mind, and inhibit a response based on the identity of a second stimulus. This is the first clear task in which there is a deficit in stimulus-stimulus, or context-dependent behavioural impairment, regardless of sensory modality (**Figure 1.4**). Control experiments showed that these impairments were not due to inability to discriminate between auditory or visual stimuli and were not due to a total loss of conditioned behavioural inhibition, suggesting to the authors

that the impairment was one of "recent memory or 'holding' capacity". A follow-up study (Cordeau and Mahut, 1964) showed that two years later, these monkeys still showed normal discrimination for objects and colours, but impaired brightness discrimination. However, the previously-seen deficit in DMS tasks was not observed years later.

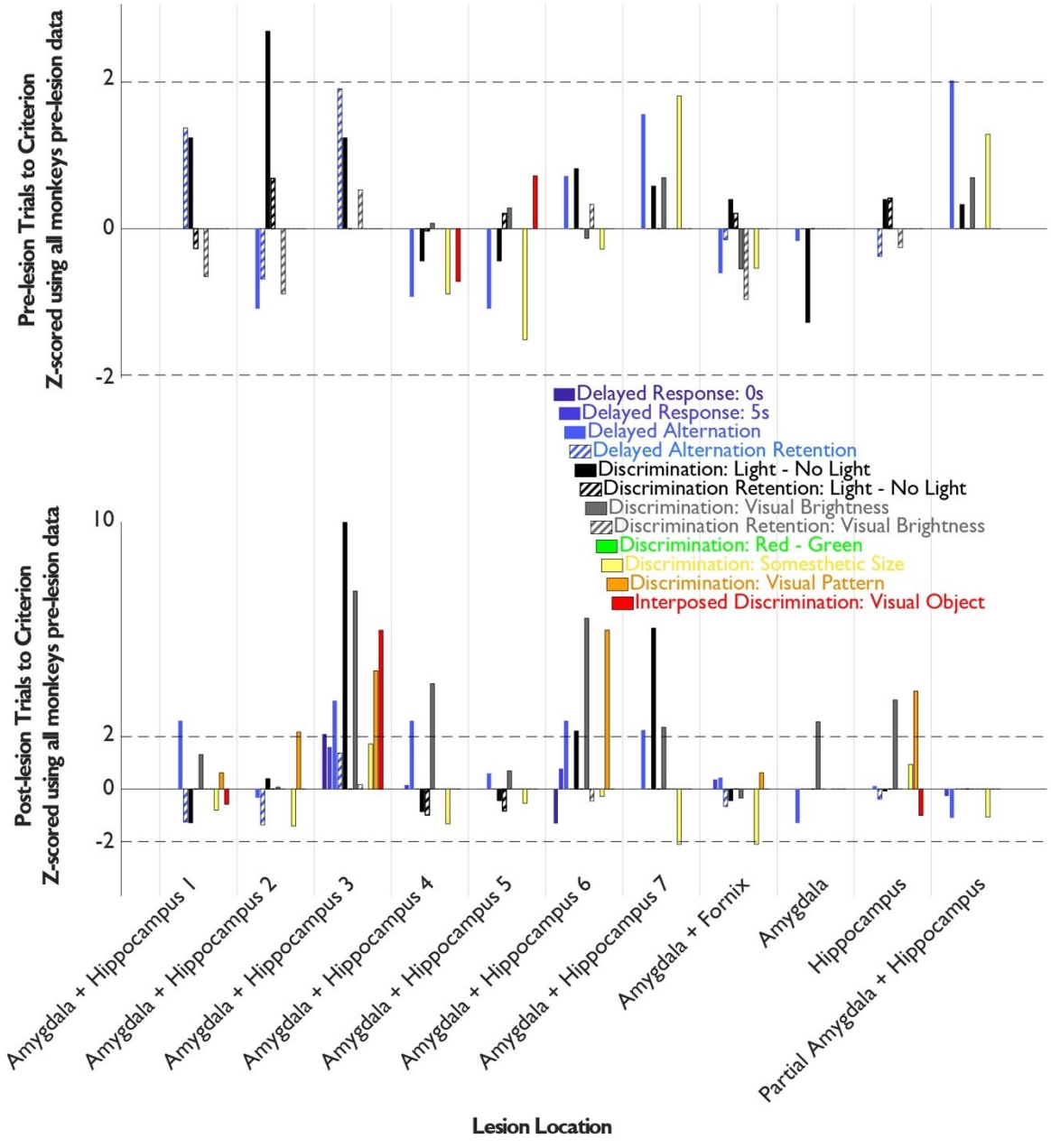


Figure 1.3. Results from Orbach, Cordeau & Rasmussen 1960

Pre-and post-lesion performance. Data extracted from (Orbach et al., 1960) and shown graphically. Note, interpretation of these results is difficult; not all monkeys were tested in all tasks, and pre-lesion tests are not necessarily repeated post-lesion. Nonetheless, these results were extremely influential and shaped understanding of hippocampal function for years. For clarity, results from monkeys without temporal lobe lesions are not shown. Tasks with no pre-lesion data were also not included. Conventions as in **Figure 1.1** and **Figure 1.2**.

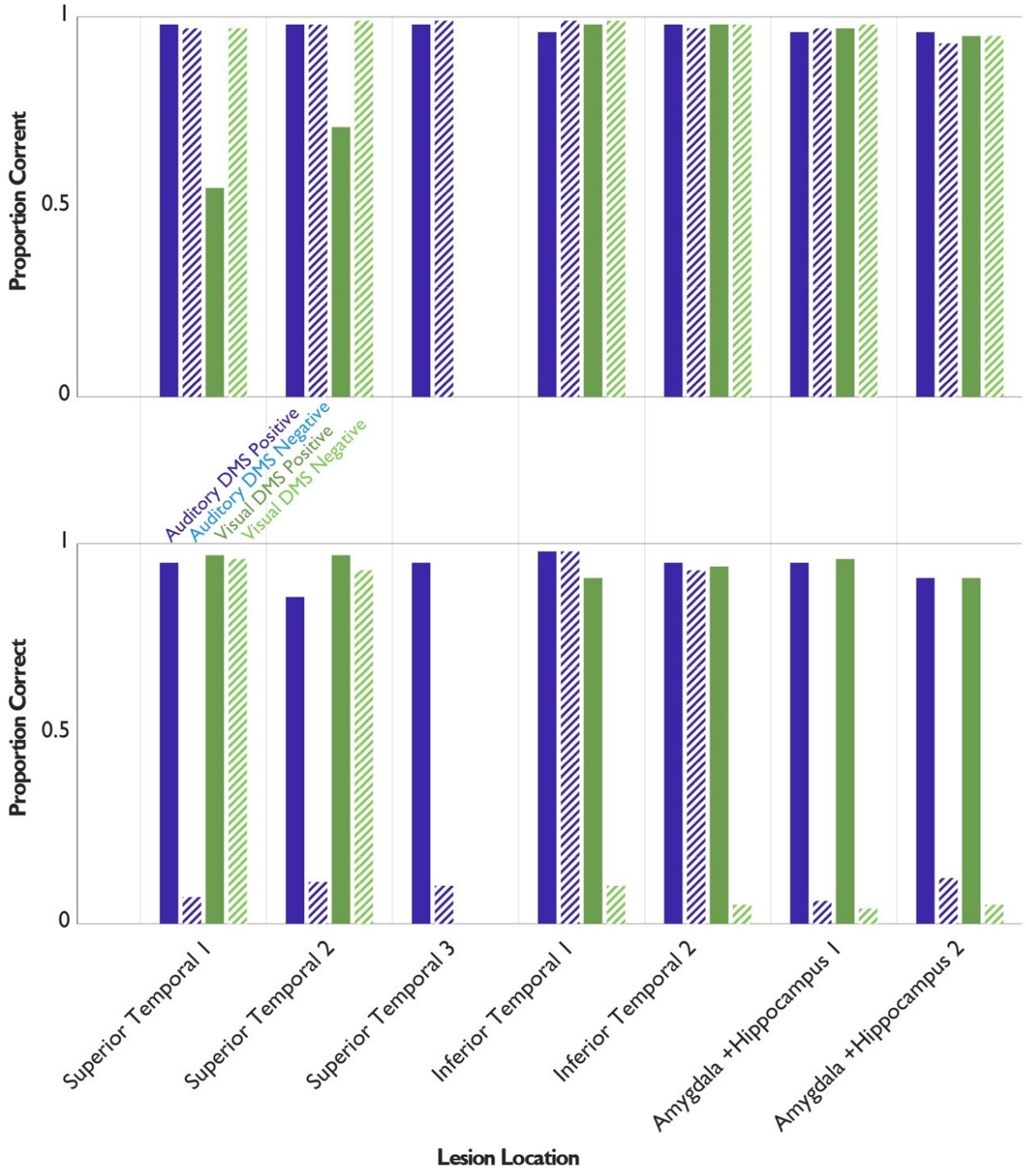


Figure 1.4. Results from Stepien, Cordeau & Rasmussen 1960

The proportion of correct trials on a delayed-match-to-sample task with auditory or visual stimuli. Data extracted from tables in (Stepien et al., 1960) and shown graphically here.

Note, in the "positive" conditions, a correct response required subjects to open the reward box when the sample matched the cue. In the "negative" condition, a correct response required subjects to avoid the reward box when the sample did not match the cue. These results show multi-modal deficits following combined ablation of the hippocampus and amygdala when the subject's response must be inhibited.

Pribram and colleagues (Pribram et al., 1962) sought to contrast the effect of lesions in the hippocampus and cingulate gyrus – both regions of the third tier of the limbic system, finding that hippocampal lesions impair performance in pre-operatively learned spatial delayed alternation, and post-operative re-learning. Authors in this case concluded that alternation behaviour was dependent on structures of the medial forebrain, as these monkeys showed coincident damage with other areas of the temporal lobe. Kimble & Pribram proposed that the wide variety of behavioural deficits seen to this point following temporal lobe ablation may be caused by a difficulty executing complex sequences of actions (Kimble and Pribram, 1963). Therefore, they aimed to determine whether two action sequences could be learned following hippocampectomy. To do this, they trained monkeys to complete a "self-ordered" sequence task (depress two panels showing a "1" in sequence, from an array of 16 panels) or an "externally ordered" sequence task (press "1" then "5" in that order). Three of four hippocampectomized monkeys could not learn the self-ordered task, and all were slower to learn the externally-ordered task. Even when two of the control animals were hippocampectomized, and they showed a retention deficit in the self-ordered task, but performed better than naive subjects on the externally-ordered task. There was no difference in discrimination learning, nor emotional changes in any lesioned animals, suggesting that indeed, short-term memory for sequences may be perturbed, while preserved performance in discrimination tasks corroborated the preservation in short-term memory seen in previous studies.

Mahut and Cordeau sought to expand upon the thesis that amygdalohippocampal lesions impair performance in DMS and DA tasks (**Figure 1.5**; (Mahut and Cordeau, 1963)). Importantly, some of the behavioural tasks used here required spatial discrimination and spatial reversal with intervening delays. Authors claimed that these results show that perturbation of the medial temporal lobe (amygdaloid complex and hippocampal formation) impairs performance in tasks that specifically involve spatial reversals, and this result was referenced in an influential text later (O'Keefe, 1978). This is the first time that a spatial role of the hippocampus was proposed on the basis primate experimental literature, even though the number of monkeys included in each group was low (2 controls; 1 inferior temporal ablation; 3 lateral temporal ablation; 2 medial temporal ablation). Similar deficits in delayed alternation but not delayed response were observed elsewhere (Correll and Scoville, 1967).

An important follow-up of HM was published in this decade, in 1968. In this, it was reported that HM showed no perceptual deficit, and was deemed to have similar performance

in perceptual discrimination to normal controls with similar visual acuity. This is in contrast with a study in other patients with temporal lobe damage (Dorff, Mirsky & Mishkin, 1965) and studies in non-human primates that did show deficits on brightness discrimination (Cordeau and Mahut, 1964) (Orbach et al., 1960). Two further studies showed comparable deficits in MS tasks learned pre-lesion (Correll and Scoville, 1965; Drachman and Ommaya, 1964).

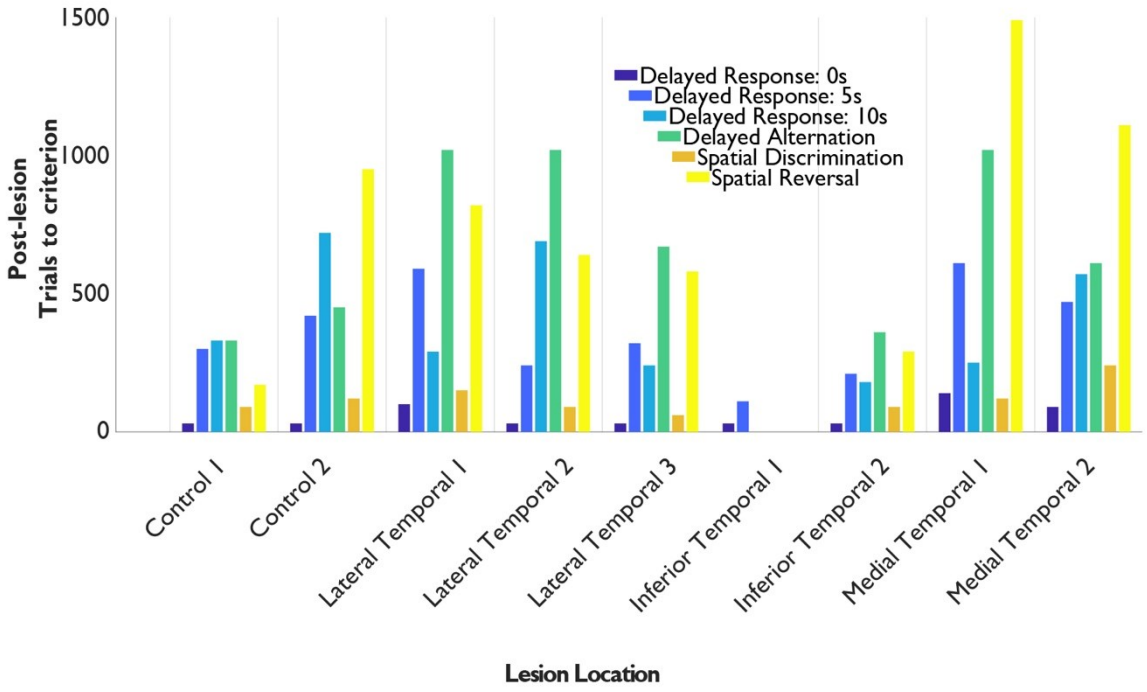


Figure 1.5. Results from Mahut & Cordeau 1963

Trials to criterion for each monkey after surgical lesion.
Data are extracted from (Mahut and Cordeau, 1963) and shown graphically here.

1.1.4.2 Single neuron recordings in the 1960s.

In the 1950s, Paul MacLean had made substantial advancements to Papez's descriptions of the limbic system. Seeking experimental support for anatomical and functional role of the hippocampus in the limbic system, he anaesthetized squirrel monkeys and recorded local field potentials from the hippocampus in a variety of conditions: with visual stimulation, olfactory bulb stimulation, cingulate gyrus electrical stimulation, and septal electrical stimulation (Gergen and MacLean, 1964). Based on the potentials recorded from different layers of the hippocampus, compared to the latency of responses to similar stimulation in the entorhinal cortex, it was concluded that photic and olfactory information is transmitted to the hippocampal pyramidal cell apical dendrites via entorhinal cortex and the subiculum. Afferents from the septum project to the basal dendrites in the stratum oriens of the hippocampus, as well as entorhinal cortex and the subiculum. A follow-up study (Yokota et al., 1967) sought to further explore the effects of septal vs sensory (olfactory) effects on single pyramidal neurons in the hippocampus. This time, intracellular and extracellular potentials of hippocampal pyramidal neurons were recorded after electrical stimulation of the olfactory bulb or the septum. It was concluded that septal input (possibly linked to the hypothalamus) can be considered interoceptive input, analogous to unconditioned stimuli in classical conditioning paradigms (since they are sufficient to evoke discharges alone). The olfactory input is exteroceptive in origin, analogous to conditioned stimuli in classical conditional that must be associated with unconditioned stimuli during learning.

1.1.5 The 1970s

1.1.5.1 Insights on hippocampal function from experiments in rodents

Two primate lesion studies from the from the early 1960s showed deficits spatial tasks (Mahut and Cordeau, 1963; Orbach et al., 1960). Shortly thereafter, and through the late 1960s, recording from single hippocampal neurons in rodents during a wide variety of behaviours became commonplace. This culminated in a succinct description of single neurons that fire action potentials when rodents occupied a specific region of a familiar environment (O'Keefe and Dostrovsky, 1971). The impact of the discovery and description of these "place cells" current theories of hippocampal function simply cannot be understated. The 1971 communication and an expounded tome on the topic (O'Keefe, 1978) ushered in a new era of hippocampal research on spatial responses of hippocampal neurons and ensembles in rodents (Moser et al., 2017). This work inspired decades of research that purports the hippocampus is

"the inner GPS of the brain", for which the 2014 Nobel Prize in Physiology or Medicine was awarded. This line of research is dominated by studies in rodents; due to technical challenges, analogous primate studies were only conducted decades later, many of which explicitly sought to corroborate these findings from rodents.

1.1.5.2 Notable lesion studies in the 1970s.

By the author's best account, at least 14 independent hippocampal & temporal lobe lesion studies were conducted on non-human primates in the 1970s.

The studies of the previous decade suggesting a special role of space in hippocampal processing were bolstered by a series of studies examining spatial- versus object- DA and DR in monkeys. Mahut and others had showed deficits in DA tasks after hippocampal and fornix perturbation in monkeys, but this was specific to spatial DA tasks (Mahut, 1972; 1971; Mahut and Cordeau, 1963; Mahut and Zola, 1973; Waxler and Enger Rosvold, 1970). Jones & Mishkin (Jones and Mishkin, 1972) employed two versions of a reversal task using a WGTA: an object reversal task, and a place reversal task. On the WGTA, two objects were presented; either a place, or an object was consistently baited. Once the animal learned the reward association, the other object or location was baited, and the reversed reward association had to be learned. Monkeys with combined lesions to the parahippocampal gyrus and hippocampus were most impaired on the place reversal task and continued to decline as the number of reversals accumulated, committing many perseverance errors. Interestingly, lesions including the temporal pole and amygdala caused impairments in both tasks; thus, the authors surmised that the role of the hippocampus in memory was modality-specific (as suggested by earlier studies), whereas the amygdala was critical for all types of stimulus-reward associations.

An innovative task showed a significant memory deficit following fornix transection (Gaffan, 1974). Recognition was intact at short delays, similar to deficits reported in amnesic patients (Warrington and Taylor, 1973). In this task, rather than a simple recognition (MS), monkeys were trained monkeys on a "list" task, wherein objects are presented serially. Therefore, the number of objects and/or time intervening the reappearance of an object (hence match-to-sample) could be varied. This was termed a serial recognition task. A second "delay" task was used, to determine whether the intervening time between object appearance and reappearance, or the intervening objects was the determining factor for performance. If the same list was used repeatedly, performance improvement was qualitatively mild in

fornix-transected animals. Improvement was qualitatively larger for control animals. Animals with fornix transection performed worse than controls if 2 or 9 objects were presented between the sample and match trials. Animals with fornix transection performed worse than controls if the delay was 70 or 130 seconds, but not at a delay of 10 seconds (Gaffan, 1974).

In one of the most resonant hippocampal lesion studies to date, Mishkin used a newly developed method in an attempt to discern a global deficit in visual memory from a deficit in visual recognition (**Figure 1.6**; (Mishkin, 1978)). To do this, he used a one-trial learning DNMS task, wherein objects presented were unique on every trial. It had been shown that this method significantly improves learning rates in monkeys by exploiting their natural tendency to explore novel objects, similar to the natural tendency to explore novel locations in monkeys and rats (Mishkin and Delacour, 1975). Because this task exploited monkeys' natural tendencies to explore novel objects, rather than amygdala-dependent (Jones and Mishkin, 1972) learned object-reward association, it was predicted that 1) damage to the

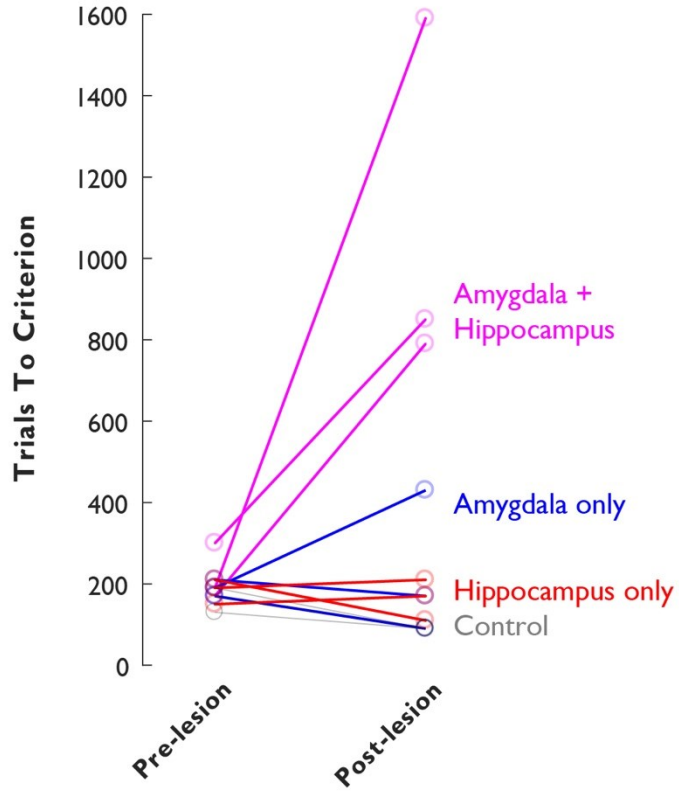


Figure 1.6. Results from Mishkin 1978

Trials to criterion for each monkey in a one-trial delay non-match-to-sample before and after surgical lesion.

Data extracted from (Mishkin, 1978) and shown graphically here.

amygdala alone would not produce a deficit, and 2) any impairments in this task could be attributed to amnesia for the objects themselves. Thus, when combined amygdalohippocampal lesions produced a specific and profound deficit, this was interpreted as monkey model of global amnesia (Mishkin, 1978).

1.1.5.3 Single neuron recordings in the 1970s.

One early single-neuron electrophysiology in monkeys offered some empirical support for hippocampal involvement in MS tasks. In conference proceedings (M. W. Brown and Horn, 1978), it was reported that 25% of hippocampal neurons were selective for the identity of the cue stimulus, and 28% of neurons were selective for the conjunction of the test stimulus and cue stimulus. Since the response of hippocampal units to the test stimulus was conditional on the identity of previous stimuli, the authors take this as proof that hippocampal activity is task-dependent; however, this claim is difficult to evaluate without a further elaboration of the results beyond subsequent conference proceedings (M. W. Brown, 1982).

1.1.6 The 1980s

1.1.6.1 Notable lesion studies in the 1980s

In this decade, at least 50 lesion studies involving the hippocampi of monkeys were published (see **Chapter 9: Appendices, I**). It had previously been reported that monkeys with hippocampal perturbation were impaired on spatial reversals, but not object reversals (Mahut, 1971). This claim was equivocated by a series of studies in the 1980s with inconsistent results in similar tasks (Gaffan and Harrison, 1984).

XX ADD Murray's lesion work, showing that hippocampal damage does not affect delayed nonmatching to sample performance in monkeys (see Baxter and Murray 2001)

"Ringo (1988) showed that apparent cross-laboratory differences in the effect of hippocampal aspiration lesions on DNMS performance were reconciled when the data were analysed using loss in d' scores" Baxter & Murray, Hippocampus 2001

In one study, it was shown that hippocampal damage perturbs object-in-place associative learning (Parkinson et al., 1988). In this study, monkeys were seated in front of a WGTA. Testing proceeded in a manner similar to the previously discussed trial-unique DNMS (Mishkin, 1978); however, the object chosen in the cue phase of the trial was positioned over two wells in the test phase. The monkey had to choose the object at the novel location. Thus, authors deemed this an object-in-place associative memory task.

Mishkin's interpretation of the "global amnesia" shown in a trial-unique DMNS task (Mishkin, 1978) were corroborated in a different modality. Monkeys with amygdalohippocampal lesions were profoundly impaired in a one-trial DNMS task using tactually- rather than visually-distinct objects (Murray and Mishkin, 1983). A novel variant of a conditional response task was also introduced. Monkeys were placed in front of a touch screen, and a trial initiated with the presentation of a white bar; after the animal touched the white bar, either stimulus A or B appeared. If stimulus A appeared, the animal had to touch the screen four times within 3 seconds to get a reward; if stimulus B appeared, the animal must not touch the screen within 3 seconds to get a reward (Rupniak and Gaffan, 1987). This task was highly influential, and also used in neurophysiological studies by Rolls and colleagues.

1.1.6.2 Single neuron recordings in the 1980s.

In the 1980s, single neuron electrophysiology studies in non-human primates started to employ the same tasks as used in lesion literature, such as a spatial DR task (Watanabe and Niki, 1985). In this paper, the greatest proportion of responsive units were active during the delay period (43%), followed by response period activity (19%), cue- and choice-lights (15%), cue lights alone (9%), choice lights alone (8%), and the presence or absence of a reward (6%). It was not reported that any of the choice-light responsive neurons were conditionally active on according to the position of the cue-light, analogous to the activity observed by Brown in the 1970s. In contrast to the prevailing conclusion of a typical lesion study of the period, the plurality of delay-period responsive units led these authors to support the hypothesis that the hippocampus is implicated in all tasks with a working memory component.

In 1989, Edmund Rolls published a set papers with hippocampal recordings in monkeys (Cahusac et al., 1989; Miyashita et al., 1989; Rolls et al., 1989), launching an influential series of experiments that extends for decades. In all three experiments, monkeys were seated inside of a custom-made chair in a large laboratory space, and performing tasks in front of a video monitor.

In the first of these studies (Miyashita et al., 1989), monkeys were trained to learn a stimulus-response association, similar to a task developed at Oxford (Rupniak and Gaffan, 1987). Monkeys were seated in front of a video monitor and response keys. Monkeys initiated a trial by pressing the central key, which was followed by an auditory tone that

signalled the monkey to attend to the screen. After the tone, one of two stimuli (A or B) appeared on the screen. For stimulus A, the monkey had to press the response key three times within 3s. If stimulus B was shown the animal had to withhold a response for 3s to obtain a reward. Monkeys completed at least 50 trials with each stimulus pair, and could be exposed to multiple stimulus pairs during the recording of a single neuron. 14% of the 905 recorded neurons were differentially active during stimulus presentation on the respond and withhold trials, and their activity was not strictly related to the motor movement (as illustrated by recording the same neuron during control tasks with other stimulus pairs).

In a separate study (Rolls et al., 1989) monkeys completed a serial object-place memory task (similar to (Gaffan and Saunders, 1985)). A series of objects was presented on the video monitor, and could appear in one of up to 9 possible locations. Monkeys had to remember the location of each object when it was first presented, and respond when it appeared at the same location, and inhibit responses when objects appeared at a different location. Across sessions with this task, experimenters recorded neurons from the hippocampus and hippocampal gyrus (entorhinal, perirhinal and parahippocampal cortices), and firing rates were analysed during stimulus presentation. ~2% of neurons responded for a combination of object novelty and place; ~10% were responsive to object place. A visual discrimination task was used as a control for sensory, motor and reward-related activity unrelated to the object-place memory task. Since neurons appeared to have place-specific responses to objects on the screen, the experimenters did a variety of behavioural manipulations to investigate the nature of these responses. Neurons were found that responded to the experimenter's position in the room when they were holding food rewards. Some neurons responded for orientations in the room (subiculum neurons only). Some neurons responded to chair rotations. In a different report with the same sample of neurons (Cahusac et al., 1989), the activity of some neurons was found to be specific to certain remembered locations.

1.1.7 The 1990s

1.1.7.1 Notable lesion studies in the 1990s

At least 53 studies examined the effect of hippocampal and temporal perturbation in monkeys this decade. With the number of primate hippocampal lesion papers expanding steadily, a consensus amongst the function of the primate hippocampus based on experimental lesions and neuropsychological testing became ever more fleeting.

The effects of hippocampal perturbation across studies testing object reversal learning were equivocal. Deficits in object reversal learning were observed in some studies after fornix transection (Ridley et al., 1992) and neurotoxic lesions (Murray et al., 1998), but not in others where aspiration or neurotoxic lesions were performed (Ridley and Baker, 1997; Ridley et al., 1995).

A follow-up study on object-in-place learning (see (Parkinson et al., 1988)) corroborated the original deficits observed after hippocampal lesion, noting that deficits were dependent on the number of places to be remembered (Angeli et al., 1993). These two studies (Angeli et al., 1993; Parkinson et al., 1988) are cited throughout this decade and the next by Rolls and colleagues as evidence that the hippocampus is critical for object-in-place learning. However, their validity is later called into question by evidence that damage to the parahippocampal cortex, rather than hippocampus impairs object-in-place learning (Malkova and Mishkin, 2003).

Single neuron recordings in the 1990s

While the effect hippocampal lesions on memory tasks in monkeys became confounded by examinations of confounding lesions to other portions of rhinal cortex through the 1990s, this decade saw the launch of a long series of non-human primate electrophysiology papers.

Several of these studies were completed by a group of researchers at Toyama University. To characterize spatial responsiveness in hippocampal neurons, monkeys were seated in front of an operant conditioning apparatus, and tested neuronal responses to auditory and visual stimuli. Visual stimuli included an apple, raisin, spider model, stick, and human actions. Auditory stimuli included harmonic rich or pure tones, a voice, a monkey cry, a step, clap, crash, and various other sounds. Monkeys were also rotated in an attempt to dissociate allocentric and egocentric spatial reference frames. Though the conditions used in this experiment were not rigorously controlled, the authors determined that approximately 10% of neurons in the monkey hippocampus were spatially-specific. A preliminary extension to this study was published twice (Ono et al., 1991a; 1991b), and ultimately years later (Ono et al., 1993a). Monkeys were seated inside a motorized cab, and an auditory cue tone was played from a speaker behind them. This cue tone informed monkeys which of four response bars to press. If the correct bar was pressed, the cab then moved to a new location, and a reward was given. At some locations, the cab was also rotated during the ITI to determine

whether neurons were place and direction selective. Visual stimuli were also presented to the monkey from a variety of directions while they were in the cab. Neurons were deemed responsive to a variety of task features. Approximately 14% were deemed place selective, though it should be noted that the statistics used were unconventional and very susceptible to spurious “place field” identification. Approximately 17% were stimulus direction selective Only one neuron of 238 recorded was observed to be position responsive and rotation invariant. The authors interpret this work as showing place-related neurons in the primate hippocampus that were analogous to those reported in rodents. A small subset of these neurons (14 of 79 place-selective neurons) were also examined during passive movement conditions (Nishijo et al., 1997). None yielded a significant correlation between firing rate maps across active and passive movement conditions.

In previously described work, Rolls and colleagues sat monkeys in front of a touch screen and performed modified versions of DA and DR tasks. In an extension to this work, similar tasks were employed while moving the monkey and/or the monitor around the laboratory to determine reference frames for spatially specific responses (Feigenbaum and Rolls, 1991). The largest proportion of neurons with spatial selectivity were deemed allocentric: the responses remained in the same position on the screen or in the room when the monkey was rotated or moved to a different position in the laboratory. This work was extended by putting a monkey chair on a wheeled trolley that experimenters could move around a laboratory manually, or under the control of a robot. The chair was on a turntable that could be at any angle relative to the linear motion. Head and body positions were fixed, but eyes could be moved with a 100° field of view from the chair, and eye position was not tracked. The largest proportion of responsive neurons were modulated by whole-body movement, and a smaller proportion responsive to combinations of movement and place or view (O'Mara et al., 1994). These view cells were interpreted as part of a memory system providing representations of a part of space that is not dependent on the position it was viewed from (Rolls and O'Mara, 1995). When monkeys’ eyes were tracked in a similar experimental set-up, reconstructions of gaze position in the environment further supported these claims that primate hippocampal neurons were spatial view cells unlike those previously observed in rodents (Georges-François et al., 1999; Rolls et al., 1997). Spatial view fields in CA1 were found to persist even when the view was partially obscured (Robertson et al., 1998).

1.1.8 The 2000s

1.1.8.1 Notable lesion studies in the 2000s

By the beginning of this decade, at least 140 studies employing lesions involving the hippocampus had been conducted in an attempt to infer neuropsychological function from observed deficits (**Chapter 9: Appendices, I**). The variability in observed effects in these studies was matched only by the variability of their experimental design. To this end, a systematic review of some of this leisure was attempted (Zola and Squire, 2001). The authors determined that several factors of experimental design that seemed to have some predictive power on the observed effect of the study were identified. These included: the extent of task training prior to hippocampal lesion; the type of surgical protocol followed; delay interval in DNMS tasks; however, the studies included in this meta-analysis precluded any conclusions about the relationship between lesion size and task performance.

A follow-up study to earlier work showing object-in-place learning deficits after hippocampal lesion (Angeli et al., 1993; Parkinson et al., 1988) was also completed using more spatially-precise neurotoxic lesions with ibotinec acid (Malkova and Mishkin, 2003). In this study, Mishkin reports that deficits he and colleagues previously observed may be attributed to inadvertent damage of the parahippocampal cortex, parasubiculum and presubiculum. Indeed, inadvertent damage to surrounding structures of the medial temporal lobe is pervasive through research decades of research dating back to Mishkin's own thesis work; for a comparison of the labels used then and most currently to report boundaries of temporal lobe damage, see **Figure 1.7**. Furthermore, a re-analysis of previous studies showed a negative correlation between hippocampal lesion size and impairment on DNMS tasks (Baxter and Murray, 2001a) (but see (Baxter and Murray, 2001b; Zola and Squire, 2001) for statistical critiques).

In another commentary, the authors argue that the all previous studies conducted using a WGTA are misinterpreted, since allocentric or egocentric spatial strategies can be alternately used to solve them. Furthermore, the authors claim, "Our experiments have shown that the primate hippocampus is unequivocally involved in the processing of allocentric, spatial relational information, thus confirming its conserved function across mammalian species" (Banta Lavenex and Lavenex, 2009).

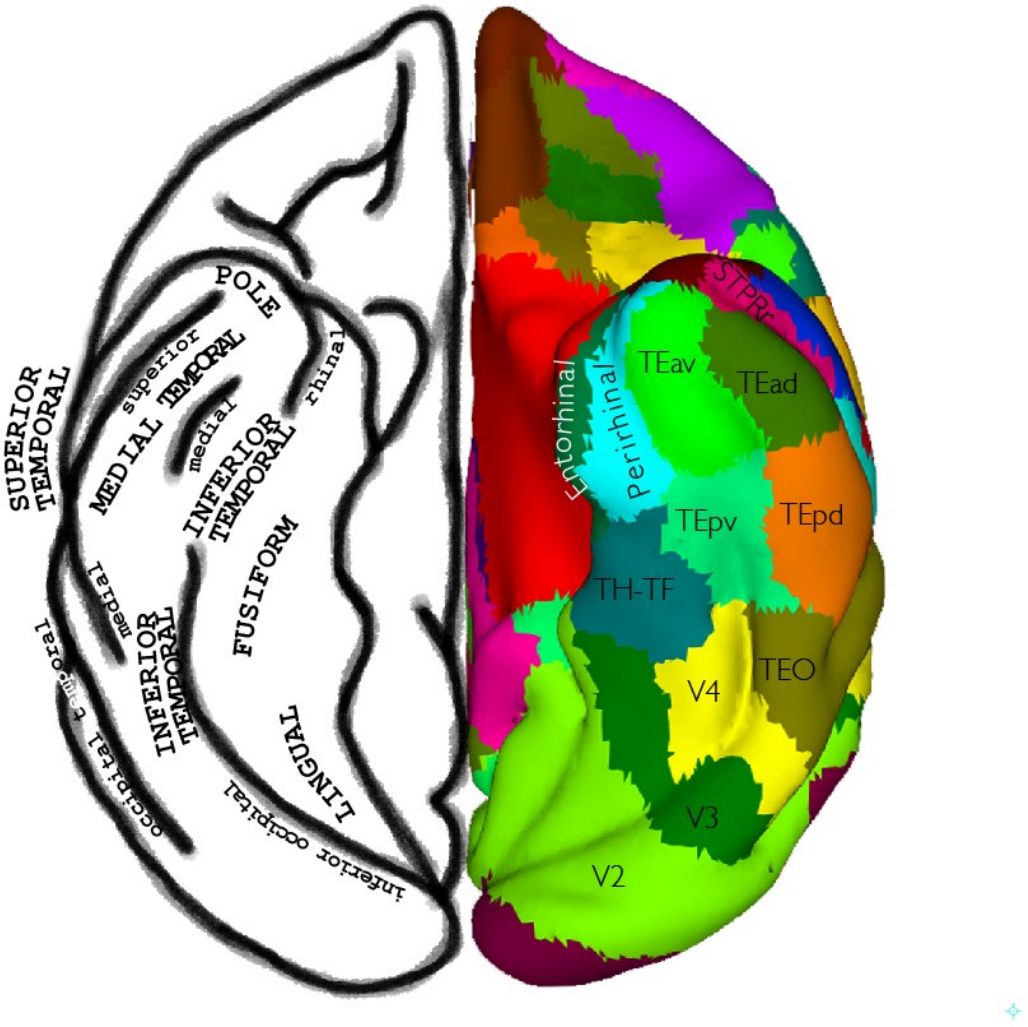


Figure 1.7. Surface anatomy of cortex surrounding the hippocampus

Brain reconstruction showing descriptions of ventral temporal cortex used in early and modern temporal lobe lesion and electrophysiology studies. Left: Ventral view of the regions (capital letters) and sulci (lower case letters) of the temporal lobe, using labels from (Mishkin, 1951). Right: Modern connectivity mapping and computational tools (Markov et al., 2014) allow for a finer parcellation of temporal lobe structures. Reconstructed using (Majka et al., 2012).

1.1.8.2 Single neuron recordings in the 2000s

Evidence for modulation of single-unit activity during learning has also been observed in NHPs. Monkeys in front of a computer screen learned novel scene-position associations, in which animals were presented with complex photographs, and were cued to respond with an eye movement to one of four possible targets (Wirth et al., 2003). Which

correct target was rewarded for each scene was learned through trial-and-error. Of 145 recorded hippocampal units, 25 units (17%) showed a significant positive or negative correlation between firing rate and trial-by-trial behavioural performance. Furthermore, the selectivity of these units was significantly modulated over the course of learning. However, doubts about the identification and isolation of single units, and an extremely low percentage of scene-viewing periods that modulated neural activity leave questions as to whether these results are indeed analogous to associative learning signals seen in rodent studies or in other NHP brain areas (Asaad et al., 1998). In other learning paradigms, hippocampal neurons that signalled trial outcome after reward delivery (or lack thereof) were also observed (Rolls and Xiang, 2005; Wirth et al., 2009).

Further studies at this time also showed spatially-selective firing of primate hippocampal neurons in a variety of paradigms. Single neurons in the temporal lobe were recorded from epilepsy patients undergoing pre-operative monitoring. During these recordings, neurons in the hippocampus and parahippocampal cortex were deemed place-specific on the basis of ANOVA testing of firing rate in across a pixelated map of the virtual environment (Ekstrom et al., 2003). Single neurons were also recorded from the hippocampi of squirrel monkeys as moved around a large cage to collect food rewards. Neurons were identified with average firing rates in some pixelated cage maps that exceeded five times the firing rate outside of that pixel (Ludvig et al., 2004). Some hippocampal neurons recorded in monkeys that were place selective using a more liberal threshold were selectively active based on the position of a navigable area in a large virtual environment (Hori et al., 2005).

1.1.9 The 2010s

Despite the wealth of research published on the topic, a holistic and universally accepted interpretation of previous hippocampal lesion studies in non-human primates remains elusive in the current decade. As one notable example, contemporary re-examination of previous hippocampal lesion studies suggests that the hippocampus is implicated specifically in recognition of scenes, rather than behaviours that are dependent on objects, places or their simple conjunction in any general sense (Murray et al., 2017).

In one highly cited example of hippocampal recordings in non-human primates, monkeys were seated in front of a computer screen while a series of images were presented in front of them (Jutras and Buffalo, 2010). Monkeys were not faced with any specific task; they were able to freely view the presented scenes with a reward schedule that was unrelated to the

task. Thus, this was termed naturalistic scene viewing. Every scene was presented multiple times. Since monkeys naturally prefer to explore novel stimuli, the amount of time spent examining repeated scenes could be compared to the amount of time spent examining scenes on their initial presentation, and the difference was used to infer whether monkeys recognized a particular scene. In this task, 24% of neurons fired differently for initial and recognized repeated scenes.

The most compelling examination of hippocampal firing rates in primates to date was recently published (Wirth et al., 2017). Authors aimed to determine the importance of active vision in modulating the firing rate of hippocampal neurons in non-human primates during goal-directed virtual navigation. Two monkeys were trained to complete a wayfinding task, in which one of five arms of a star maze was consistently rewarded. Animals started each trial in a non-rewarded arm, and used the landmarks to inform navigate back to the rewarded goal arm. This paper was the first to combine analyses of heading direction, gaze position, and recent actions in primates. Neurons exhibited a wide variety of tuning to parameters that included allocentric spatial position, gaze position, head direction and a combination of these variables and recent actions termed “state space”. A proportion of neurons contained significant information content for all of these factors; nearly all of the neurons with significant information for any of these factors contained significant information content for state space. From this, the authors concluded that hippocampal neurons contain abstract, multidimensional representations because some cells firing rates are different between “action contexts” (Wirth et al., 2017).

1.2 A conciliatory consensus: Two theories of hippocampal function

A wide variety of experimental paradigms and findings have been covered to this point, and this represents only a fraction of all literature presented in **Chapter 9: Appendices, I** and **Chapter 9: Appendices, II**. Despite the breadth of this research, the overwhelming conclusion of this literature is currently that the hippocampus serves two cognitive functions: episodic memory and spatial navigation (Buzsáki and Moser, 2013; Eichenbaum and N. J. Cohen, 2014; Ekstrom and Ranganath, 2017; Schiller et al., 2015).

1.2.1 The hippocampus and memory

The hippocampus initially proposed to play a role in memory based on its diverse anatomical connectivity early in the 19th century (Meyer, 1971) and this was later supported

by temporal lobe lesion studies in monkeys (S. Brown and Schäfer, 1888). This relationship came into much finer focus with electrical stimulation of the medial temporal lobe (Penfield, 1958a) and contemporary observations that bilateral ablation of the hippocampus caused deficits in recent memory and anterograde amnesia (Milner and Penfield, 1955; Penfield and Milner, 1958; Scoville, 1954; Scoville and Milner, 1957). Lesions that include the hippocampus or fornix cause analogous deficits in recognition and associative memory in monkeys (Gaffan, 1994; Mahut and Zola, 1973; Mishkin, 1978; Zola-Morgan and Squire, 1985). Consistent with lesion studies implicating the hippocampus in recognition memory, subsets of hippocampal neurons have been shown to respond differently to novel and familiar objects at certain locations (Cahusac et al., 1989; Jutras and Buffalo, 2010; Rolls et al., 1989). Furthermore, changes in selectivity of hippocampal neurons correlate with behavioural changes (Wirth et al., 2003) and trial outcome during associative memory tasks (Rolls and Xiang, 2005; Wirth et al., 2009). In humans, hippocampal neurons respond differentially during initial and subsequent stimulus presentations in a recognition task (Fried et al., 1997), and responses during initial presentation are predictive of subsequent recognition (Cameron et al., 2001; Suthana et al., 2015). Hippocampal neurons encoding a stimulus are also re-activated prior to free recall (Gelbard-Sagiv et al., 2008). Taken together, a wealth of literature from studies in primates shows that perturbations of cortex that include the hippocampus also perturb performance in a variety of memory tasks, and the firing rates of individual hippocampal neurons change as a function of learning during associative memory tasks. The strong implication is that the hippocampus instantiates some processes that are critical for neuropsychological functions that require associative memory (Eichenbaum, 2017a; Penfield, 1958b).

1.2.2 The hippocampus and space

Proceeding in parallel to the aforementioned line of research, some studies of primate hippocampal neurons aimed to correlated changes in firing rate to action in space, objects in space, or position in space *per se*. Initially, primate hippocampal neurons were reported to fire for specific motor responses (Watanabe and Niki, 1985; F. A. Wilson et al., 1990) or stimulus direction (Tamura et al., 1990). When spatial relationships between subjects and stimuli were changed, some neurons were found to encode stimulus location egocentrically, or allocentrically with reference to location in the room or on the video monitor used to show stimuli (Feigenbaum and Rolls, 1991). If monkeys moved around a room, hippocampal neurons were found to respond to rotation, translation, place, and view

(O'Mara et al., 1994; Rolls and O'Mara, 1995). In motorized cabs, hippocampal neurons were found to be task-responsive and place selective (Ono et al., 1993b), and that neuronal responses changed with experimenter-controlled movement (Nishijo et al., 1997) or subject-controlled cursor movement on a monitor (Hori et al., 2003; Matsumura et al., 1999). Spatially specific firing has also been observed in monkeys foraging for reward inside of cages (Ludvig et al., 2004). In experiments that record subject position and gaze position in the environment, hippocampal neurons and parahippocampal neurons are selective specifically for spatial view (Georges-François et al., 1999; Rolls et al., 1997), and spatial view fields in CA1 persist even when obscured (Robertson et al., 1998). During virtual navigation, hippocampal neurons can be selective for place and view in humans (Ekstrom et al., 2003; Miller et al., 2013), as well as the configuration of extramaze cues in monkeys (Furuya et al., 2014; Hori et al., 2005). Furthermore, place-specific firing of hippocampal neurons in monkeys can be different during passive movement, and dependent on the previous sequence of actions leading to the place field (Wirth et al., 2017). An emergent consensus from this body of research is that spatial representations in the hippocampus can be modulated by a variety of environmental, cognitive, and behavioural factors.

1.3 The Missing Links & the Present Investigation

Arising from parallel descriptions of the hippocampus as a spatial and mnemonic processing area, a few major questions arise: Is position in space the primary variable that these neurons are encoding? Could it be that other parameters of behaviour explain what these neurons are encoding? What is the relationship between neuronal correlates of spatial position and confounding elements of an experience related to memory rather than a veridical representation of space? Though place cells in the primate hippocampus have been observed, it is not known whether these neurons can maintain a veridical representation of space in the primate hippocampus. Furthermore, the extent to which sensory and mnemonic components of cognitive tasks can drive spatial specificity has not been investigated in primates.

The broad goal of the present thesis is to test some fundamental tenets of theories that the function of the hippocampus is to mediate spatial navigation or memory. Specifically, whether and how the hippocampus encodes space in a virtual environment will be examined. Furthermore, the nature of the paradigm developed herein allows for the examination of encoding of objects that are critical to associative memory in the virtual environment.

1.3.1 Aim 1: Characterize spatial encoding in the primate hippocampus

In *Aim 1* of this monograph, I will examine spatial encoding by hippocampal neurons in non-human primates. This will be done across behaviours in an otherwise stable environment. Within this aim, I hypothesize that classical analyses of spatially-specific activity will yield descriptions of "place cell" analogues in the monkey hippocampus. However, I further hypothesize that the spatial specificity of these neurons will be task-dependent. To test this, I have recorded the activity of single hippocampal neurons from the right posterior hippocampi of monkeys while they complete two cognitive tasks in a common virtual environment. I examine the specificity of hippocampal spatial coding within and across tasks, showing that similar proportions of monkey hippocampal neurons can be classified as place cells using common statistical metrics. However, the hippocampal code for space does not generalize across tasks.

1.3.2 Aim 2: Characterize sensory and mnemonic encoding across spaces

Aim 2 of this monograph builds upon the finding that the hippocampal code for space is task-dependent in monkeys. Thus, I examine whether the neural activity in large regions of space correlates with sensory and mnemonic representations that could be confounded with spatial representation. Within this aim, I hypothesize hippocampal neurons encode elements of the environment examined in Aim 1 that inform the monkeys' behaviour in that space. To test this, neural activity is examined with respect to trial-varying features of the cognitive task using forwards and backwards encoding models, showing that sensory and mnemonic representations of trial features are present and dynamic across trial periods.

1.3.3 Aim 3: Characterize object-specific encoding as a function of learning and memory

In *Aim 3* of this monograph, I will examine whether foveated objects are encoded by non-human primate hippocampal neurons, and whether encoding of these objects changes with learning. I hypothesize that the features of the environment (goals, and cued contexts) that inform subjects' choices will be disproportionately represented in hippocampal neurons, and that these representations will co-occur with learning of the associations between these environmental features. To test this, hundreds of thousands of foveations identified during task completion was parsed, so that firing rates and the objects foveated during each one could be further analysed. I show that a subset of hippocampal neurons fires preferentially for

every object visible in the environment (not just those relevant to guiding behaviour), and that these representations do indeed change with respect to learning in the environment.

Taken together, the aims and outcomes presented in this monograph suggest that there are key predictions of each neuropsychological theory of hippocampal function that are not fully and neatly corroborated using the activity of all hippocampal neurons recorded. Thus, theoretical implications, practical implications, and directions for future informed studies are discussed.

2 General Methodology

2.1 Experimental subjects

All experiments described herein were conducted with the participation of two male monkeys (*Macaca mulatta*; 7 years old, 7 kg; 14 years old, 12 kg). All animal procedures complied with the Canadian Council of Animal Care guidelines and were approved by the McGill University Animal Care Committee. Monkeys received food rewards as positive reinforcement at the beginning and end of each experimental session. Behavioural patterns and body weights were closely monitored to ensure stable health conditions throughout the experiment. These monkeys were trained to perform behavioural tasks described below, and given juice reward for their efforts in each task (400-1000+ mL daily).

2.2 Experimental Set-Up

During training and experimental sessions, the monkeys were seated in a custom-built chair in front of a computer monitor. While seated, the head position of the monkey was fixed. This facilitated eye position tracking and eye movement classification, as described in **Section 2.2.1**, as well as intra-hippocampal recordings described in **Section 2.2.2**.Eye position was monitored at 500 Hz via video-based eye tracking (EyeLink 1000, SR Research, Ontario, Canada). The chair was fit with a two-axis joystick that the monkeys used to complete behavioural tasks in virtual reality environments, as described in **Section 2.2.3**. Player position within the virtual environment was updated and recorded at 75 Hz, matching the monitor refresh rate.

2.2.1 Eye movement tracking and classification

Eye calibration was done at the start and end of every session using a cued saccade task. In the cued saccade task, monkeys were trained simply to fixate on a 1° visual angle (dva) white dot that could appear at any of 9 locations on the monitor in a 24 dva by 18 dva grid. A custom toolbox was created to parse eye signal collected via video oculography into saccades, fixations, smooth pursuits and post-saccadic oscillations (Corrigan et al., 2017). Briefly, the initial identification of putative saccades is done by: 1) iteratively calculating a saccade acceleration threshold; 2) grouping threshold crossings within 40ms into a putative saccade; and 3) ignoring putative saccades group shorter than 10ms. The remaining segments of eye signal were further classified by foveation type.

For all putative saccadic periods, the maximum velocity was calculated, and then the onset and offset precisely identified by comparing the main direction and inter-sample

changes in direction. Saccade boundaries were defined when the signal was either above a high threshold (60°) for one sample, or above a low threshold for three consecutive samples (20°). This method differentiates between eye movement types, since saccade direction is very consistent, whereas camera noise leads to higher inter-sample variance during smooth pursuits and fixations. Once saccades were identified, the direction and amplitude were calculated based on the onset and offset points for all saccades during the visually-guided task, including inter-trial-intervals, and for all completed trials in both virtual navigation tasks. These saccades were used for analyses of saccade direction selectivity. Saccade offset locations were used to analyse gaze position selectivity on the screen.

2.2.2 Electrophysiological Recordings

In these experiments, activity from 183 individual neurons from in superior aspect of the right mid-posterior hippocampus was recorded (predominantly CA3; see **Figure 2.1**, **Figure 2.2**, and **Figure 2.3**). Trajectories were planned and verified during electrode insertion using MRI-guided neuro-navigation (**Figure 2.1A** & **B**). Within each recording session, neuronal activity and the monkey's gaze were recorded while subjects were seated in front of a computer monitor in a custom chair. The chair was fitted with a two-axis joystick that monkeys used to complete two tasks that required virtual navigation in a custom-built virtual reality environment.

The entire protocol for planning surgical procedures, recording from the hippocampus and verifying electrode locations is schematized in **Figure 2.1**.

Prior to any surgical procedures, a naïve 500um isotropic T1-weighted 3T MRI was taken for each animal (**Figure 2.1**, step 1). Using these scans, head post placement and chamber trajectory were planned using an MRI-guided neuro-navigation suite (Brainsight, Rogue Research, Montreal, QC) (**Figure 2.1**, step 2). Chambers were positioned over prefrontal cortex, such that electrode trajectories were perpendicular to the long and transverse axis of the right middle-to-posterior hippocampus. Following surgical implantation of the head post and recording chamber, a CT scan was acquired with cannulas passing through the chamber grid at cardinal locations (**Figure 2.1**, step 3). The resultant CT and MRI were co-registered, so electrode trajectories and terminal recording locations could be specifically mapped to chamber grid holes (**Figure 2.1**, step 4).

All data was collected over the course of 37 recording sessions. In each session, hippocampal activity was recorded using up to four single high-impedance tungsten

electrodes (0.4-1.5 MOhms) simultaneously. Prior to every recording session, electrode trajectories were mapped to the MRI, and expected distances to grey and white matter were measured (**Figure 2.1**, step 5). These expected waypoints were compared against changes in neural activity while the electrode was lowered to the terminal recording site (speed 0.01mm/s; **Figure 2.1**, step 6). Distances to putative CA3 recording sites were adjusted online as necessary.

Neurons from the hippocampus were isolated while subjects sat quietly in the dark recording room, since hippocampal neurons typically exhibit elevated firing rates in this state compared to foraging or other exploratory behaviours. Local field potentials were monitored for bouts of theta-like activity and changing low frequency power profile as a function of arousal. Multi-unit activity was monitored for sparse activity and burstiness characteristic of hippocampal pyramidal neurons. Hippocampal activity was recorded at 30,000 Hz using a multi-channel recording system (128 channel Cerebus Data Acquisition System, Blackrock Microsystems, Utah, USA) for sorting and offline analysis. Cluster-cutting to isolate neurons from multi-unit clusters was done using Plexon software (Offline Sorter, Plexon Inc., Texas, USA). Cluster cutting was done agnostic to time; however, neurons with continuously morphing principle components and/or a complete loss of activity as a function of time were excluded from analyses. Any neurons with task-invariant reward-related activity were excluded from analyses.

In one monkey, post-recording verification of electrode trajectories was possible. This was done using a 350um isotropic susceptibility-weighted 7T MRI (**Figure 2.1**, step 7, cool colour map). This scan was co-registered to the naïve 3T anatomical MRI, and shows a high degree of concordance between the expected and actual trajectories and terminal recording locations.

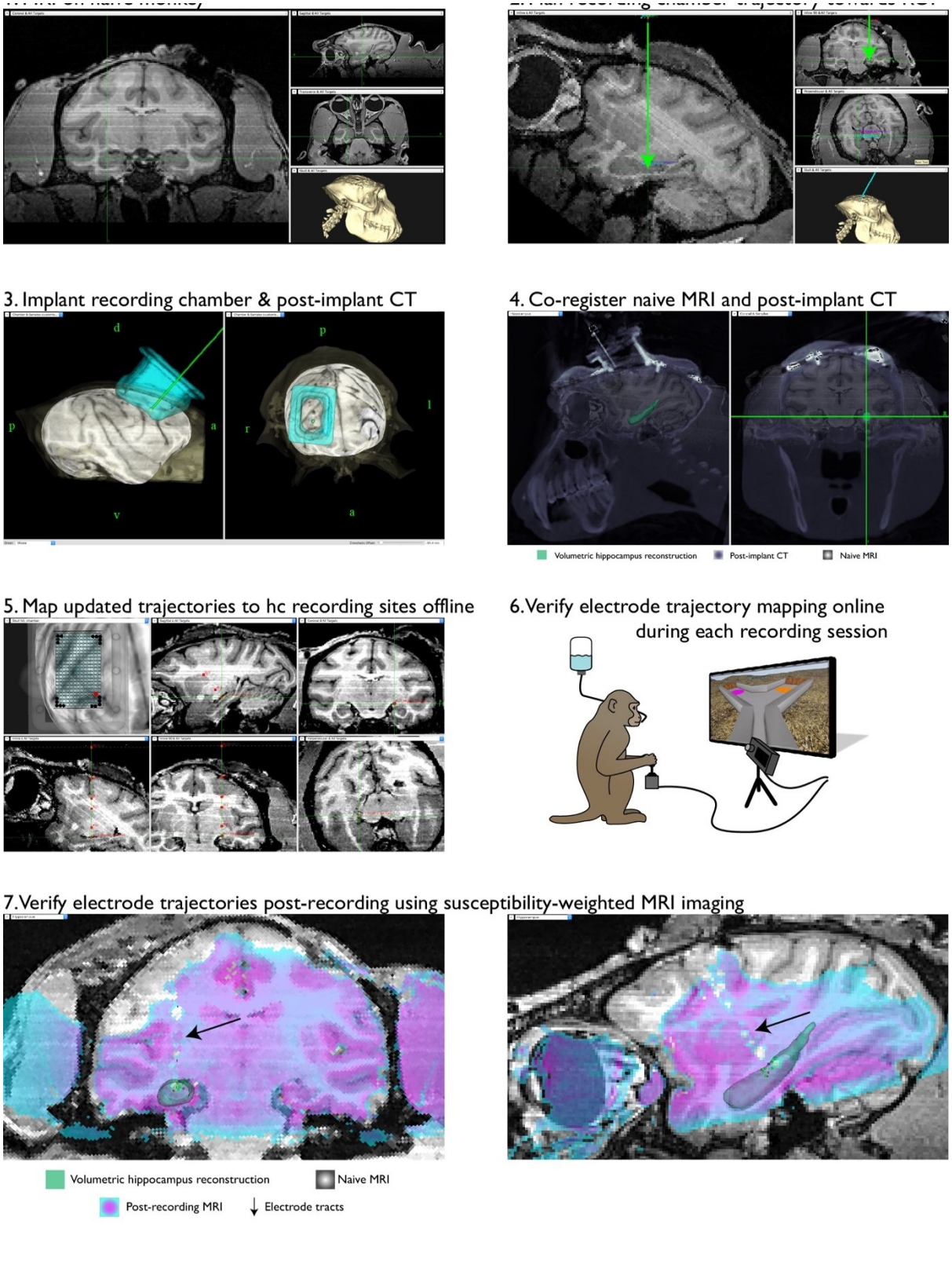


Figure 2.1. Hippocampal recordings: planning, mapping and verification

Schematic representation of the major steps in planning, mapping, and verification of electrode trajectories and recording sites.

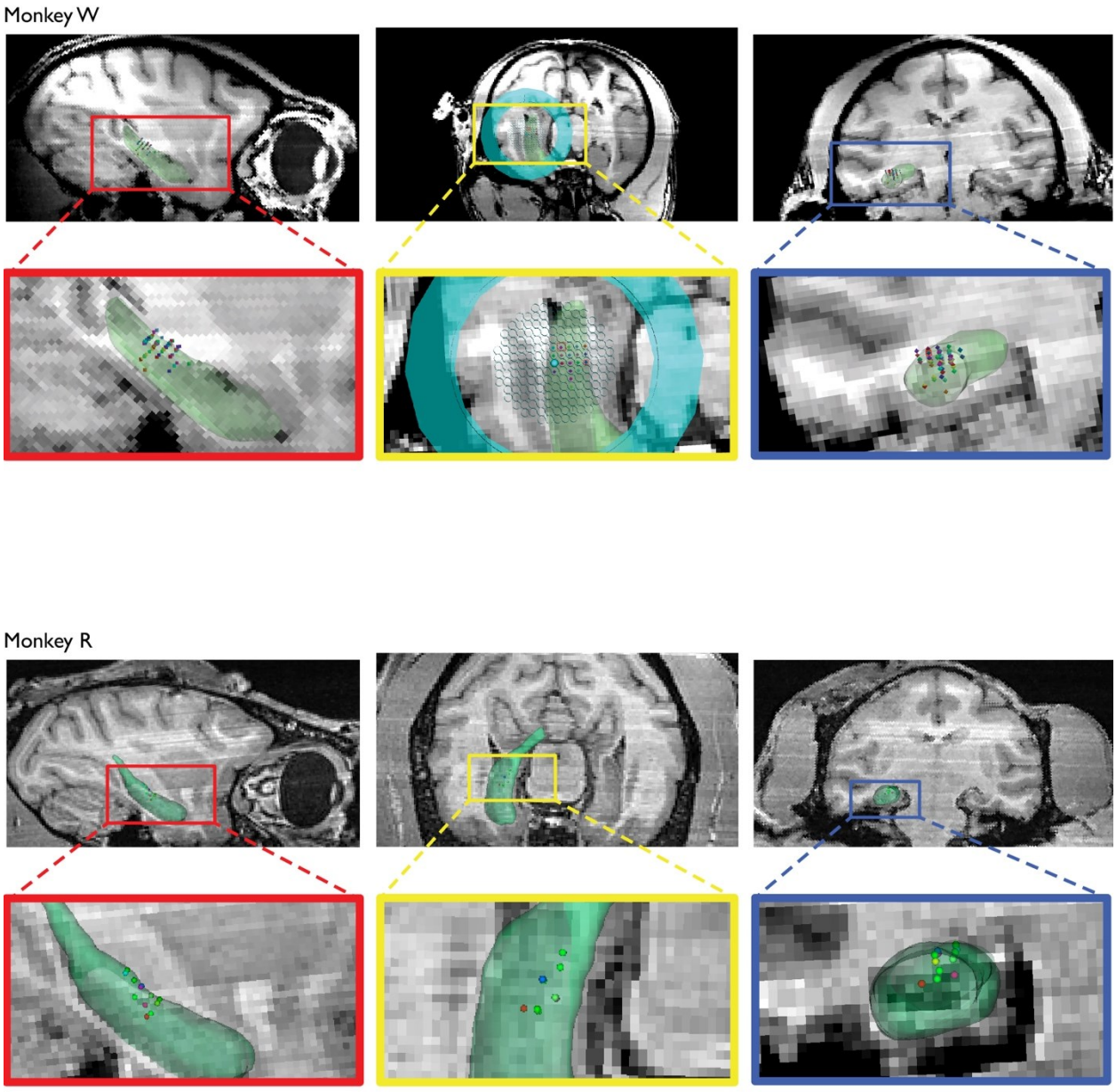


Figure 2.2. Hippocampal recording locations for each monkey

A total of 183 neurons were recorded across 37 experimental sessions.

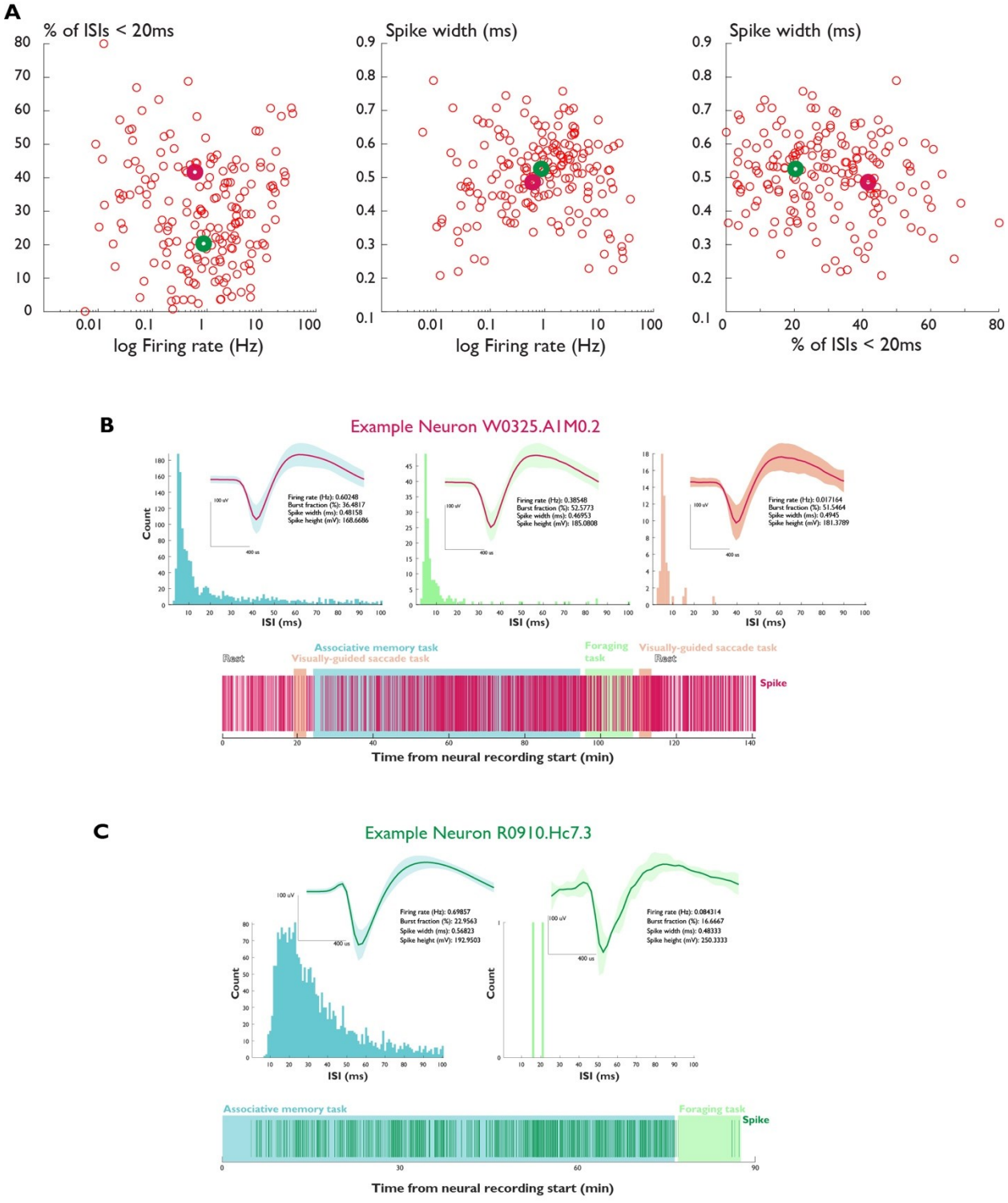


Figure 2.3. Individual neuron characteristics and example neurons

A) Burst fraction, spike width, and firing rate of all recorded neurons (n = 183). Purple and green circles mark the example neurons shown in (B) and (C), respectively.

B) Example neuron W0325.A1M0.2 inter-spike-interval distribution and average waveform. Shaded area, SEM.

C) Example neuron R0910.Hc7.3 inter-spike-interval distribution and average waveform. Shaded area, SEM.

2.2.3 Behavioural Tasks

In each session, the VR tasks were bookended by a cued saccade task wherein monkeys were rewarded for making saccades to small white dots on a grey screen (**Figure 2.6**). This task was used to calibrate and validate accuracy of eye-on-screen position and examine whether hippocampal neurons exhibit screen position or saccade direction selectivity. For the remaining two tasks, an entirely new platform was created that allows for experimental tasks to be embedded into virtual reality environments (Doucet et al., 2016). Briefly, monkeys were seated in front of a computer monitor in a chair that was fit with a customized galvanized steel joystick typically used in heavy equipment operation (part 212S15S8383; PQ Controls, Inc., Bristol, CT). Monkeys used the joystick to navigate through the virtual environment that built using a video game engine (Unreal Engine, Epic Games, Inc., Rockville, MD) and so that parameters of the behavioural tasks could be monitored and controlled in real-time via Matlab (Mathworks, Inc., Natick MA). The system architecture and control diagram can be seen in **Figure 2.4.**

The virtual environment built for these experiments is termed the X-Maze (**Figure 2.5**). This environment was created with notable considerations. First, the environment was designed to accommodate an embedded two-alternative forced-choice task, analogous in structure to **T**- and **Y**-mazes used in rodent behavioural studies for decades (Dember and Fowler, 1958; Tolman, 1948). Second, to facilitate a sense of immersion in the virtual environment, the maze must be reflected, so that it was a "double-ended" design. Thus, subjects could perform a choice trial at one end, turn around and navigate through a linking corridor, and perform a choice trial at the other end with the same local environmental structure. Third, on the sides of the linking corridor, distinct landmarks were placed on either side of the maze; thus, for all parts of the trial except when the subject is deciding to enter the right or left maze arm at either end, allocentric cues were available to orient the subject to their unique position in space. Even when these allocentric cues are not necessary to inform behaviour in any way, it has been reported that they are attended and useful for creating allocentric cognitive maps of the environment in rodents (O'Keefe, 1978).

2.2.3.1 Virtual foraging task

In the virtual foraging task, animals navigated through the X-Maze towards a red volume to receive a juice reward (**Figure 2.6**, bottom right; https://youtu.be/aWvheMzxMJo). The target could appear at any of 84 locations in the environment (dotted locations for

display purposes only), and randomly repositioned at a different location every time the subject reached it.

2.2.3.2 Virtual associative memory task

In the associative memory task, monkeys navigated the same X-Maze to learn a reversed two-context, three-object reward value hierarchy embedded into the X-Maze (**Figure 2.6**, middle right; **Figure 2.7**; https://youtu.be/RHx9Lw65oDw). Reward value associations were dependent on environmental cues (textures applied to maze walls; Context 1 and Context 2) and three differentially rewarded coloured discs (objects A, B and C). Object reward values were context-dependent; that is, in Context 1, object A > B > C, and in Context 2, object C > B > A (**Figure 2.7**). Object colours were pseudo-randomly selected from a seven-colour set at the beginning of each session to prevent repetition of colours across neighbouring sessions. Thus, a new context-object hierarchy was learned every day.

On a single trial, subjects start at either the North or South end of the X-Maze. They then navigated through a long central corridor towards the opposite end of the maze. One of two possible textures (wood or steel) was applied to some walls of the maze when the monkey reached the corridor (**Figure 2.7 B** & **C**, position a). When subjects reach the end of the corridor, they reach a forked decision point, with each of the two arms containing one of the three possible coloured objects (**Figure 2.7 B** & **C**, position b).

Each trial, the context was independently randomized, as was the object colour combination. Object colours were randomly assigned to either the left or right arm of the maze, and the same two colours could not appear in each arm of the maze on a single trial.

Quantities of juice reward given for successful completion were fixed between the cued saccade task, foraging task, and middle reward value of the associative memory task.

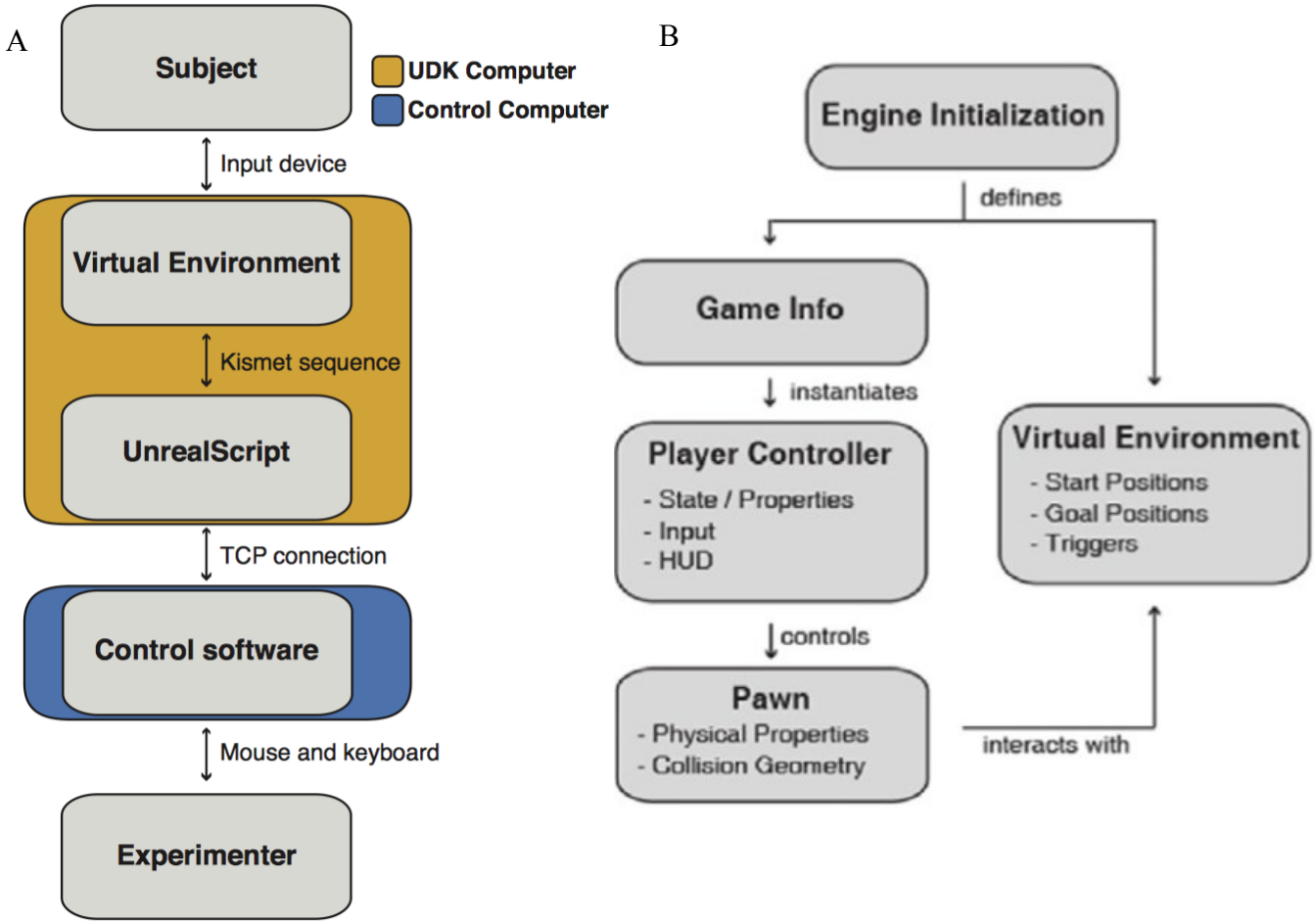


Figure 2.4. Architecture and control diagram for virtual reality toolbox

A) Detailed system architecture. Subject actions in the virtual environments first trigger UnrealScript execution through Kismet sequences. Experimental data is then exchanged between the UDK computer (blue box) and the control computer (gold box) via a network connection. On the other hand, the experimenter can trigger changes in the virtual environment by modifying task settings in the control software.

B) Engine initialization cascade. The Game Info class defines the subclasses to use for any specific task while the virtual environment contains all the geometry and usable objects.

Modified from (Doucet et al., 2016) with permission.

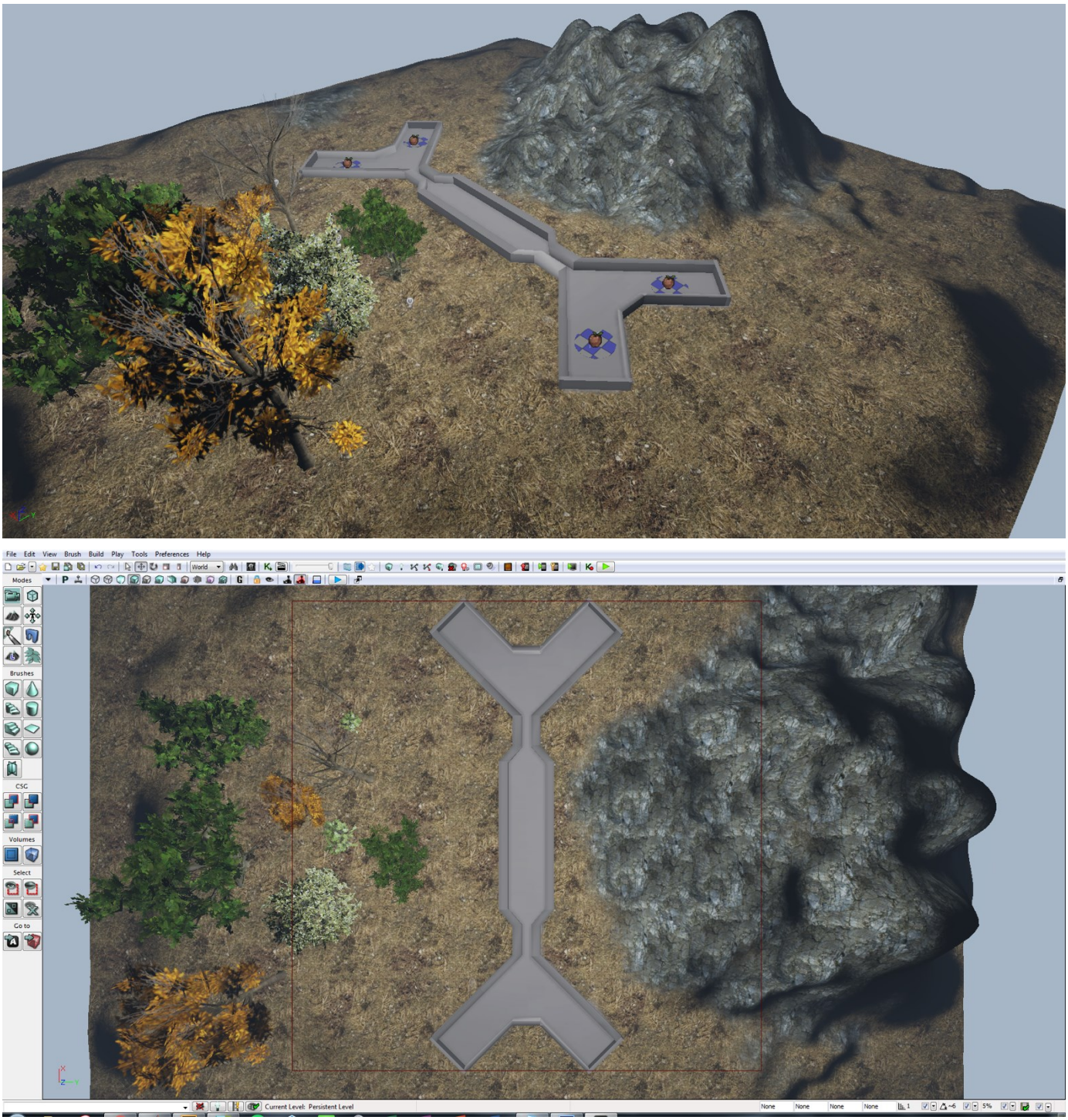


Figure 2.5. Overhead and oblique views of the X-Maze

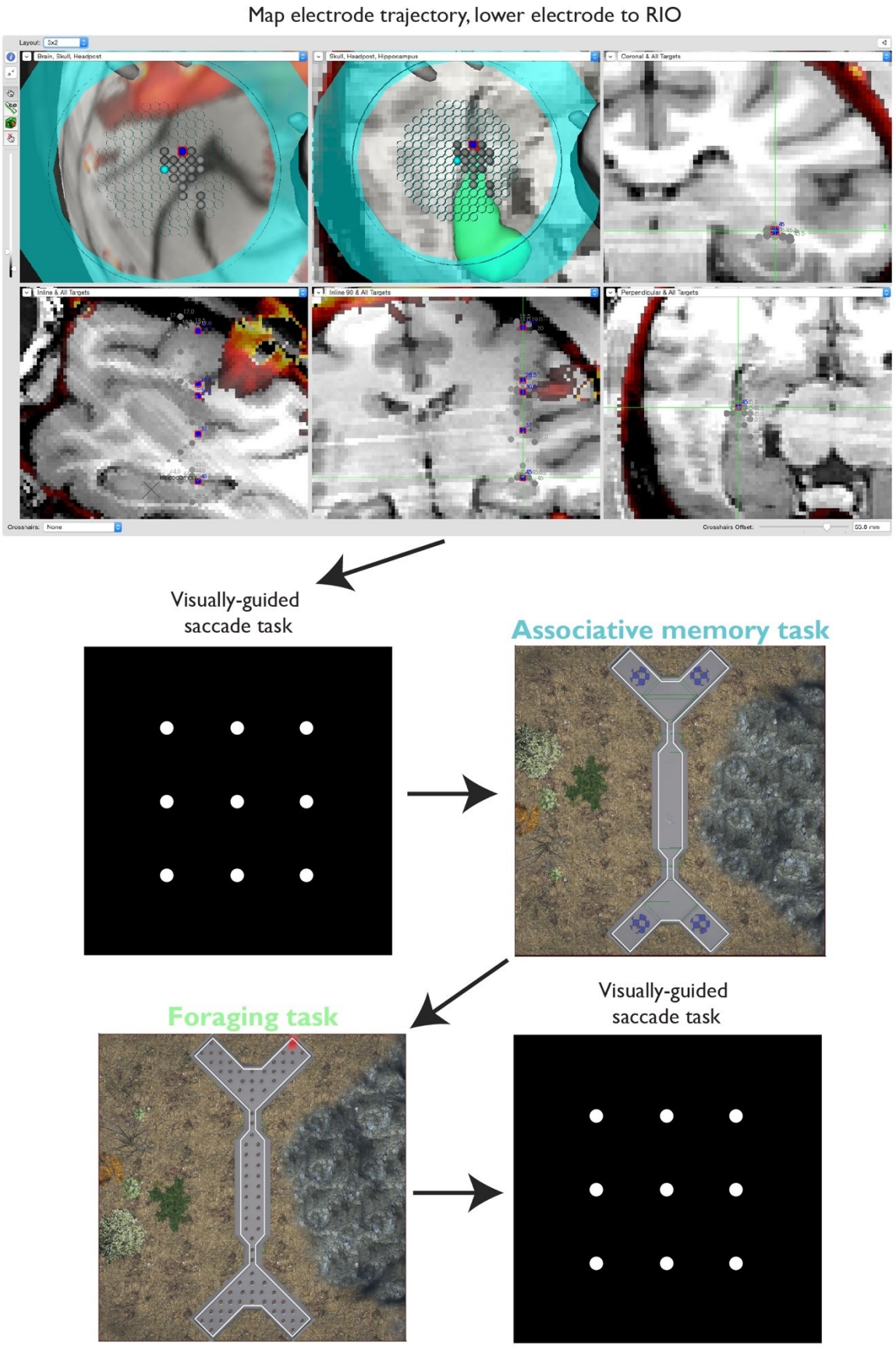


Figure 2.6. Order of tasks within a recording session

Electrode trajectory mapping was done *a priori*. Altogether, the experimental procedures typically lasted 4-6 hours per session.

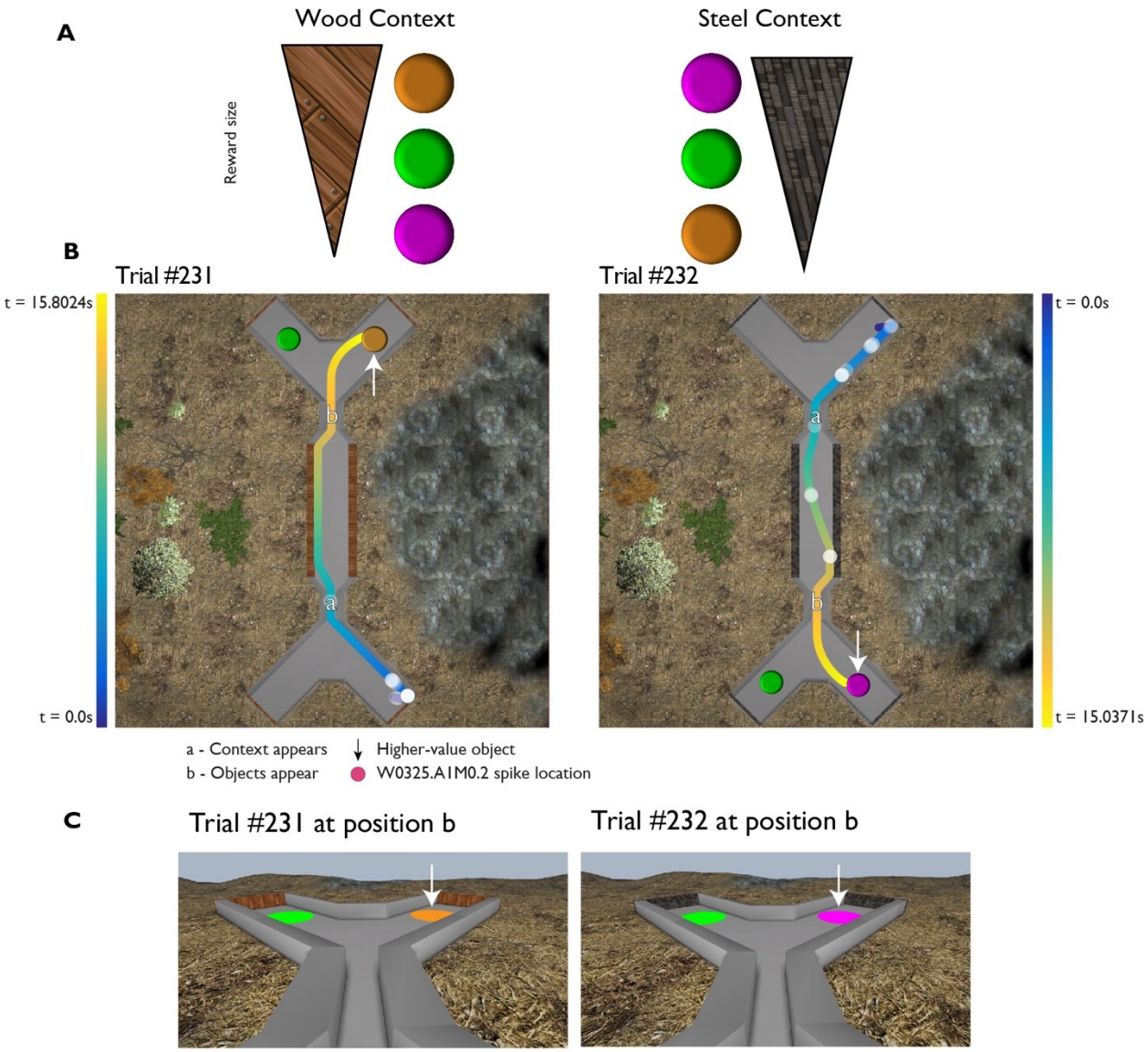


Figure 2.7. Associative memory task reward hierarchy

A) Example of the reversed two-context, three-object reward value hierarchy for recording session W0325.

B) Two example trials from the recording session. Subject trajectories through the maze are colour according to the time from trial start (colour bar). White arrow indicates the object of higher reward value.

C) Approximate first-person-view of the monkeys during each trial at position b. White arrow indicates the object of higher reward value.

D) Estimated learning state averaged for the high-low value context-dependent association across all sessions, and 95% confidence interval of this estimate.

3 SPATIAL INFORMATION IN THE HIPPOCAMPUS

"While the rodent literature has strongly supported the spatial/cognitive map theory, the primate lesion literature has generally moved off in a different direction."

Nadel, L. The hippocampus and space revisited. Hippocampus ***1,*** *221–229 (1991).*

3.1 Synopsis

Chapter 1: Literature Review introduced modern theories of hippocampal function in spatial navigation and memory. To examine these functions, non-human primate electrophysiology provides a useful experimental system in detail. **Chapter 2: General Methodology** describes several novel advances made in preparation for the work in this thesis to facilitate recording from individual neurons in the monkey hippocampus while subjects complete two tasks in a virtual environment.

In this chapter, some central tenets of spatial mapping theories are tested. Though place cells have been observed in primates, it is not known whether these neurons support a veridical representation of space in the primate hippocampus. Furthermore, the extent to which sensory and mnemonic components of cognitive tasks can drive spatial specificity has not been investigated in primates. Monkeys were trained to complete a foraging task and an associative memory task in the same virtual environment. Several analytical techniques are employed to show that individual neurons encode information about space in each task. Furthermore, the population of neurons could be used to accurately "read out" positions in the maze in each task. However, there are notable differences in the distribution of spatially selective response fields across tasks; furthermore, the population code for space in the maze did not generalize across tasks.

This chapter suggests that any spatially-specific firing observed in the monkey hippocampus may be task-dependent; therefore, a closer examination of hippocampal neuronal activity with respect to behaviour in space is warranted.

3.2 Methodology

3.2.1 Saccade Direction Selectivity

To examine saccade direction selectivity, eight 45° direction bins were created, starting with a centre on 0°. A bin was only analysed if there were at least 7 saccades in it, and a neuron's saccade direction selectivity was only analysed with a minimum of 5 saccade direction bins. Firing rate was calculated for the 150ms prior to saccade onset to get the average spike rate for each direction.

Significant direction selectivity for each neuron was assessed using a permutation test. Firing rates and directions were randomly shuffled 1000 times, generating 1000 null distributions for each saccade direction for each neuron. A neuron was categorized as being

selective for a direction if it had a spike rate that was in the top 5th percentile of the null distribution after Bonferroni correction (alpha = 0.05/number of direction bins).

3.2.2 Gaze Position Selectivity

Each on-screen foveation was categorized within one of nine 12°×8° screen areas. For each foveation within each screen location, a neuron's firing rate was calculated in the 200ms after saccade offset. Also, for a location to be included, there needed to be at least 7 saccades per location. Foveation location selectivity was tested in each task for all neurons, with enough Foveations in at least 6 screen locations in each task. Like saccade direction selectivity, gaze position selectivity of each neuron was assessed using a permutation-derived null distribution.

3.2.3 Place Selectivity

To determine whether each neuron fired more action potentials than expected by chance in any area of the X-Maze in each task, a statistical permutation test based on spatial position and spike rasters for each neuron was used (**Figure 3.1**). First, the X-Maze was parsed into a 32×12 grid of pixels. For each trial, a vector of player positions (occupied pixel number) was created at 1ms resolution. For each recorded neuron, a corresponding binary vector was produced with 1ms resolution, denoting the presence or absence of an action potential. By collapsing across trials, the occupied time and number of recorded action potentials was computed. To determine if this number was significantly above chance for each pixel, the vector of occupied pixels was circularly shifted for each trial, and the firing rate in each pixel was re-computed. This circular shuffling procedure was done 1000 times. Any pixel with an empirical firing rate exceeding percentile 1-alpha was statistically significant, where alpha=0.05/total number of occupied bins. Pixels with a total occupancy of less than 200ms were excluded. Place fields were defined as any of the 9 architecturally distinct maze areas (4 arms, 2 branches, 3 corridor sections; see **Figure 3.3** and on) with at least one statistically elevated spatial bin.

Figure 3.1. Schematic of circular shuffling procedure used to identify pixels with elevated firing rates

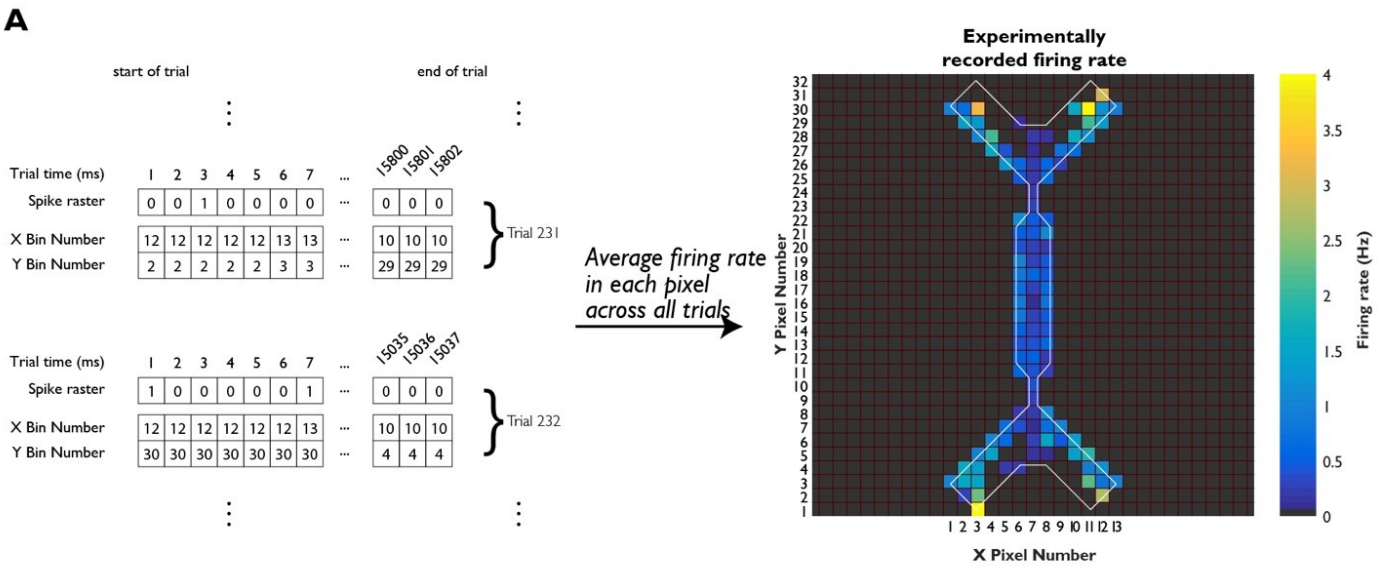
(next page)

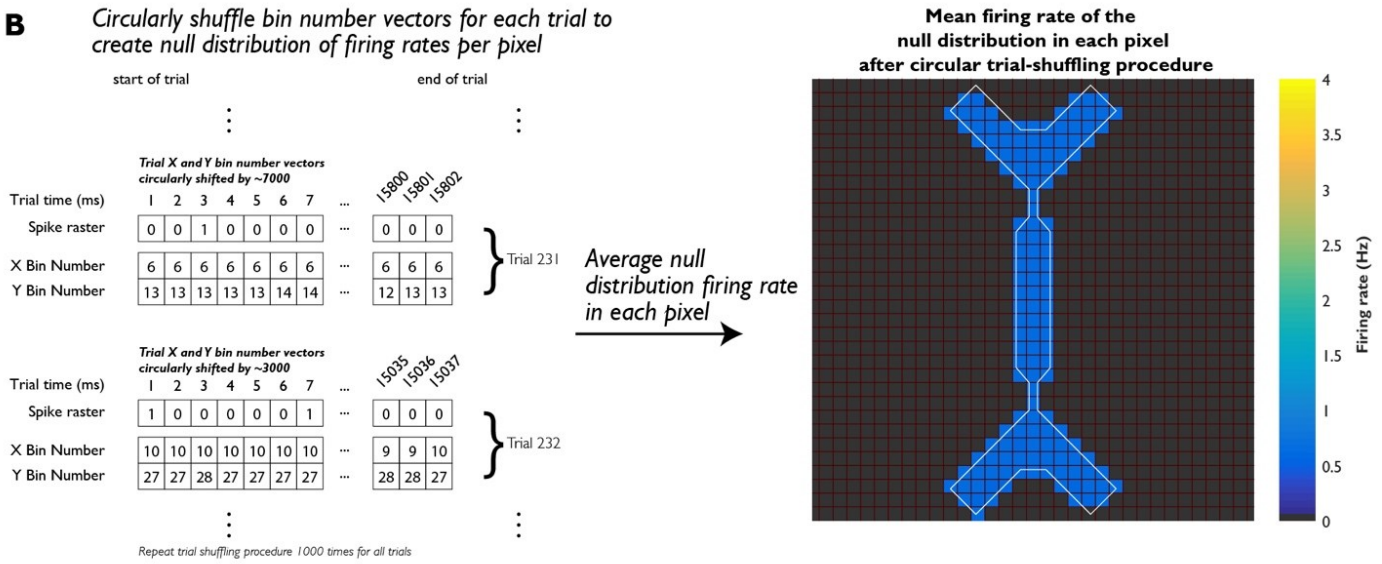
(A) For each trial, a 1ms resolution vectorized spike raster and subject position matrix was prepared. These can be used to compute an empirical spatial firing rate map, as seen for an example neuron during the associative memory task.

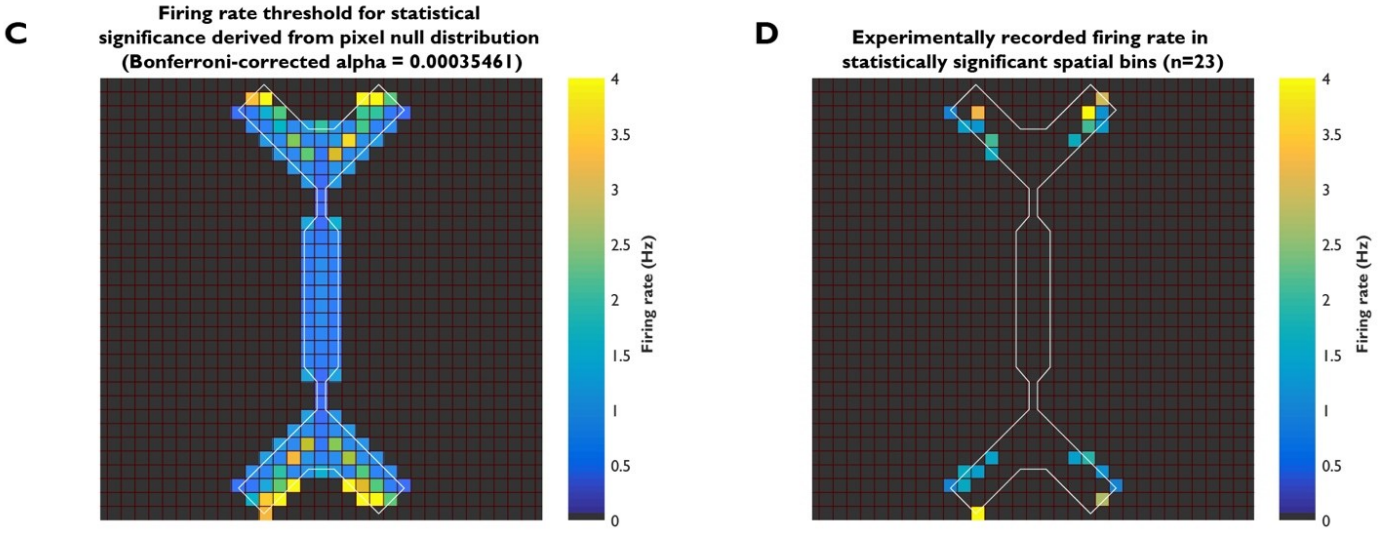
(B) A null distribution of firing rates in each pixel can be computed by circularly shuffling the subject position matrix for each trial. The mean firing rate of the null distribution for all pixels is nearly uniform.

(C) The Bonferroni-adjusted 95th percentile of the null distribution of firing rates for each spatial bin is variable, largely because of differences in occupancy per pixel.

(D) Empirical firing rate in spatial bins that exceeded the Bonferroni-adjusted 95th percentile of the null distribution.


A
start of trial
end of trial
Trial time (ms)
Spike raster
X Bin Number
Y Bin Number
Trial 231
Trial 232
Average firing rate in each pixel across all trials
Experimentally recorded firing rate
Y Pixel Number
X Pixel Number
Firing rate (Hz)


B
Circularly shuffle bin number vectors for each trial to create null distribution of firing rates per pixel
start of trial
end of trial
Trial X and Y bin number vectors circularly shifted by ~7000
Trial X and Y bin number vectors circularly shifted by ~3000
Trial time (ms)
Spike raster
X Bin Number
Y Bin Number
Trial 231
Trial 232
Repeat trial shuffling procedure 1000 times for all trials
Average null distribution firing rate in each pixel
Mean firing rate of the null distribution in each pixel after circular trial-shuffling procedure
Firing rate (Hz)


C
Firing rate threshold for statistical significance derived from pixel null distribution (Bonferroni-corrected alpha = 0.00035461)
D
Experimentally recorded firing rate in statistically significant spatial bins (n=23)
Firing rate (Hz)

The specificity of each neuron's spatial response map was quantified using spatial information content (**Figure 3.6;** (Ravassard et al., 2013; Skaggs et al., 1993). Each neuron's information content (*I*; in bits) is defined as

$$I = \sum_{i}^{L} P_i \frac{\lambda_i}{\bar{\lambda}} \log_2 \frac{\lambda_i}{\bar{\lambda}}$$

where the proportion of occupied time in each pixel (P_i) is defined as

$$P_i = \frac{o_i}{\sum_j^L o_j}$$

and the average firing rate per pixel $\bar{\lambda}$ is

$$\bar{\lambda} = \sum_{i}^{L} P_i \lambda_i$$

Spatial information content was computed for each neuron for each pixel occupied for more than 200ms. A null distribution of spatial information contents (and corresponding null spatial information maps) was computed for each neuron by circularly shifting the vector of occupied pixel numbers 1000 times prior to computing the spike rate maps for that neuron. Neurons with summed spatial information content exceeding the 95th percentile of the null distribution were deemed statistically significant, and these are included in **Figure 3.6**. Particular pixels with spatial information content exceeding that of their 95th percentile (Bonferroni-corrected for the number of occupied bins) were deemed statistically elevated, and displayed in the spatial histogram in **Figure 3.6**.

3.2.4 Spatial Classification Analyses

We used a linear classifier (Fan et al., 2008) to determine whether the population of all recorded neurons could reliably encode position in the maze (**Figure 3.7**). The same procedures were used for all spatial classification analyses, starting with firing rates for all neurons in all trials and respective conditions (i.e. "trials" could refer to passes through each spatial bin or individual trial periods in the associative memory task). All neurons that did not have at least 10 trials in all conditions were excluded from our analyses (n=152 included). To begin, 10 trials were randomly subsampled from each condition for each neuron, creating an ensemble subsample. For subsequent classification, a linear kernel support vector machine was used, cross-validated with stratified k-folds. Specifically, the ensemble subsample was

split into five stratified groups of trials (five folds), with four folds constituting the training set, and one fold reserved for testing. At this point, the firing rate of each neuron in all k-folds were z-scored using the mean and standard deviation of the training set only for that neuron (not the testing set). A linear kernel model was fit to the ensemble subsample using L1-regularized L2-loss support vector classification. An important benefit of using L1 regularization is automatic parameter selection on the model inputs; whereas L2 regularization yields parameter weights very close to zero, L1 regularization instead shunts weights directly to zero. This results in a trained model that is both sparse and more interpretable. The trained model was subsequently tested on the reserved testing fold to assess prediction accuracy. The procedure for normalization, model training and testing was repeated five times total, so each k-fold of the ensemble subsample was used as the testing set once. The entire procedure — starting from the 10-trial ensemble subsampling — was repeated 100 times, yielding a total of 500 iterations of the SVM testing procedure.

A permutation procedure was used to determine chance prediction accuracy in all cases. This proceeded similarly to the training and testing procedures described above. However, after creating the ensemble subsample and prior to splitting the ensemble subsample into stratified k-folds, the condition labels were randomly permuted, and classification analyses then proceeded exactly as previously described. This procedure was repeated 20 times for each ensemble subsample, yielding a total of 10,000 individual iterations of the SVM testing procedure.

It is important to note that each neuron's firing rate was z-scored in the training set only and within each task independently prior to classification. This negates the possibility of spurious similarity of cross-task classification models attributed to within-neuron similarity in baseline firing rates across tasks, independent of area-specific changes in firing rate. Similarly, this negates the possibility of spurious dissimilarity of cross-task classification models attributed to within-neuron changes in baseline firing rates across tasks, independent of area-specific changes in firing rate.

3.2.5 Statistical evaluation of classifier performance

The mean and standard deviation classification accuracy reported herein include testing of each individual k-fold. Significant differences between accuracy distributions were tested using a two-sample Kolmogorov Smirnov test, Bonferroni-corrected for the total number of distribution comparisons.

Classification model reliability was further evaluated using Cohen's kappa statistic (J. Cohen, 1960). The kappa statistic is an objective measure of classification reliability. Unlike raw or chance-normalized prediction accuracy, kappa provides a meaningful metric with which to compare the performance across classifiers — even with uncommon numbers of classes — because it is a bound statistic that relies on the observed and expected proportion of correct predictions for each class of a model; it is agnostic to the number of classes being differentiated. It is described as

$$\kappa = \frac{p_o - p_e}{1 - p_e}$$

where p_o is the proportion of correct predictions, and p_e is the probability of guessing the correct class by chance.

3.2.6 Spatial Classification with Neuron Drop-Out

The spatial classification analyses with dropout were carried out according to the same procedures. Spatial decoding was done starting with the entire population of 152 neurons, using the direction-dependent reference frame during the associative memory task. Additionally, for the drop-out procedure, on each iteration, the neuron with the highest spatial information content (as computed above) was removed from the population, until spatial classification analyses were run with on a single neuron. The partial population accuracy was deemed to be below that of the full population when the mean decoding accuracy of the partial population first dropped two standard deviations below the mean decoding accuracy for the entire population (denoted on **Figure 3.8** with a †).

3.2.7 Cross-task model comparison

To determine whether each neuron's contribution to the ensemble code space was similar across tasks, the model weights assigned to each neuron in each maze area were compared across the direction-dependent position classification models for each task (**Figure 3.9**). This was done using the Pearson correlation coefficient. These results were corroborated using linear regression,

$$y_i = \beta_{0i} + \beta_{1i} x_i + \varepsilon_i$$

where y describes changes in model weight for each neuron as a function of task (x_i) in each of the maze areas (i; 1, arm towards branch; 2, branch towards corridor; 3, corridor towards branch; 4, branch towards arm; 5, arm towards goal). Fit parameters (β_0, β_1) describe the intercept and slope of the regression line for model weights across tasks in each maze area, respectively, and ε estimates the residual.

"Cross-task model similarity" was reported as the Pearson correlation coefficient of model weights for each neuron across tasks (rho, **Figure 3.9**). Variance reported is the 99% confidence interval (alpha=0.05/number of trial periods) after bootstrapping 10,000 times. Trial periods with 99% of rho values not including 0 were deemed statistically significant. Using the F-statistic of the regression parameter β_1 yielded a qualitatively identical result.

As mentioned previously, each neuron's firing rate was z-scored in the training set only and within each task independently prior to classification. This negates the possibility of spurious positive correlations in each neuron's model weights across tasks related to within-neuron similarity in baseline firing rates across tasks, independent of area-specific changes in firing rate. Similarly, negates the possibility of spurious negative correlations in model weights across tasks attributed to within-neuron changes in baseline firing rates across tasks, independent of area-specific changes in firing rate.

3.3 Results

3.3.1 Single neuron firing rates are tuned for spatial position in both tasks

To characterize place-selectivity in individual neurons, the virtual environment was spatially binned into an isometric two-dimensional pixel grid covering the entire maze. In each task, occupancy time and number of spikes observed were used to compute empirical per-pixel firing rates for each neuron. A wide variety of spatial distributions of spikes could be seen across neurons and across tasks (**Figure 3.2 A**); changes in spatial distribution of activity were not due to changes in neuronal isolation (**Figure 2.3**). Across all neurons, firing rates were higher in the branching points and arms of the maze during the associative memory task than during the foraging task (**Figure 3.2 B**).

To determine which pixels' empirical firing rates were higher than expected by chance, spatial position (pixel number) and neural activity were vectorized with 1ms resolution in each task (similar to (Ravassard et al., 2013); see **Figure 3.1** and **Section 3.2.3**). The neural activity vector was circularly shifted to change the spike location on each trial

1000 times, creating a permutation-derived null distribution of firing rates for each pixel, each neuron, and each task. The number of neurons with firing rates that are statistically elevated (alpha=0.05/number of occupied pixels for that neuron in each pixel and in each task can be seen in **Figure 3.3**. The X-Maze was then divided into 9 similarly-sized areas for further analyses (4 maze arm areas, 2 branch areas, 3 corridor areas). Spatial response fields for each neuron were defined as any of the 9 maze areas with statistically elevated firing in one or more pixels.

In the foraging task, 55.7% of neurons had spatial response fields in at least one maze area (102/183 neurons, median 1; **Figure 3.4 A**, green bars, and **Figure 3.4 B**) with a uniform distribution throughout the maze ($p=0.91$, $\chi^2(8) = 3.29$; **Figure 3.3**, left column). In the associative memory task, 70.0% of neurons had spatial response fields. In contrast with the foraging task, these were not homogeneously distributed throughout the X-Maze ($p<1\times10^{-7}$, $\chi^2(8) = 52.3$; **Figure 3.3**, right column; **Figure 3.4 A**, blue bars, and **Figure 3.4 B**). Of all neurons with spatial response fields in both tasks (49.7%; 91/183), neurons were likely to gain fields in the arms and branching points of the maze during the associative memory task compared to the foraging task (**Figure 3.4 C**). The distribution of pixels with significantly elevated firing rates in each task, as well as comparisons of individual neuron place field locations within and across tasks with pixel sizes four times larger can be seen in **Figure 3.5**.

One possibility is that place-specific firing can be ascribed to selectivity for eye-on-screen position (Killian et al., 2012) coupled with biased gaze behaviour within or across tasks. Saccade direction and gaze position selectivity in all three tasks was compared for neurons with sufficient numbers of saccades and fixations in all tasks (n = 92 neurons; **Section 3.2.1**). In the cued saccade task, foraging task, and associative memory task, 7.6%, 41.3%, and 42.4% of neurons were selective for saccade direction, respectively. In these three tasks 28.2%, 43.4%, and 72.8% of neurons were selective for gaze position. Critically though, no neurons were selective for the same saccade direction across tasks, and only 2 neurons (2.2%) were selective for at least one gaze position across all tasks. Thus, saccade direction and gaze position invariably affect only a small proportion of hippocampal neurons and cannot explain the dramatic changes in spatial selectivity across tasks.

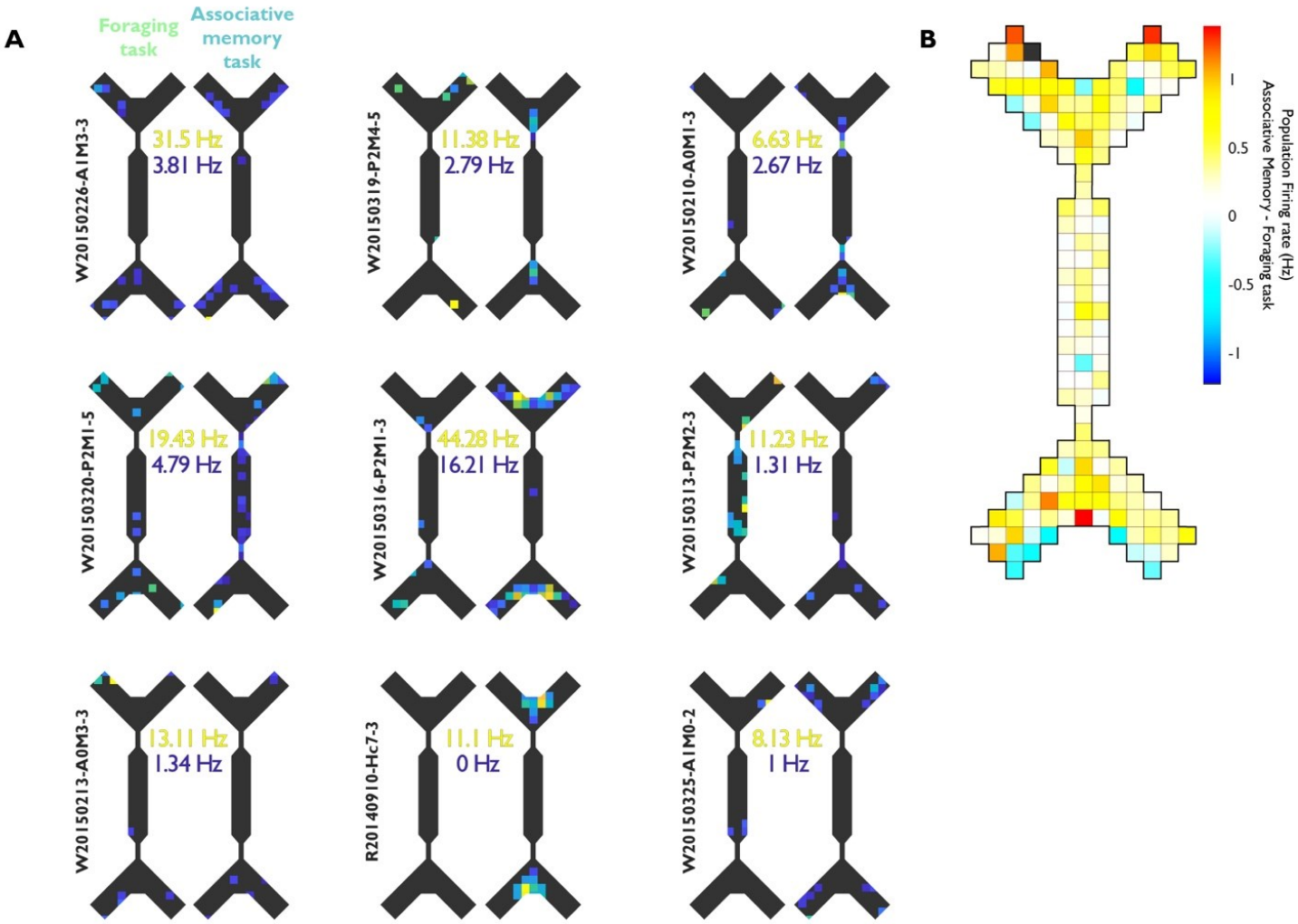


Figure 3.2. Example neuron firing rates during the foraging and associative memory task

A) Nine neurons with spatially-specific firing in the foraging (left) and associative memory (right) task. Spatial map of total time spent in each map pixel (left/first column), trial-by-trial spike locations along the north-south dimension (second column), number of spikes in each pixel (third column), and per-pixel firing rate (right/fourth column)

B) Average cross-task firing rate difference for all neurons

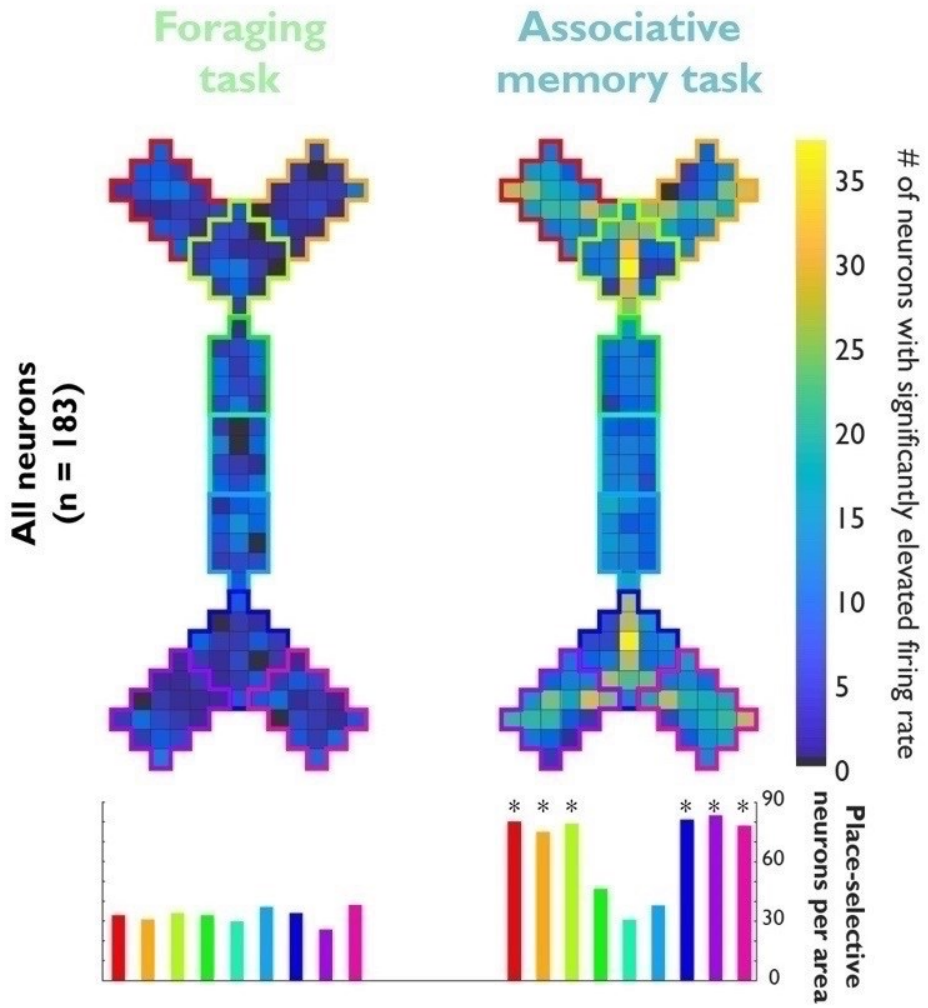
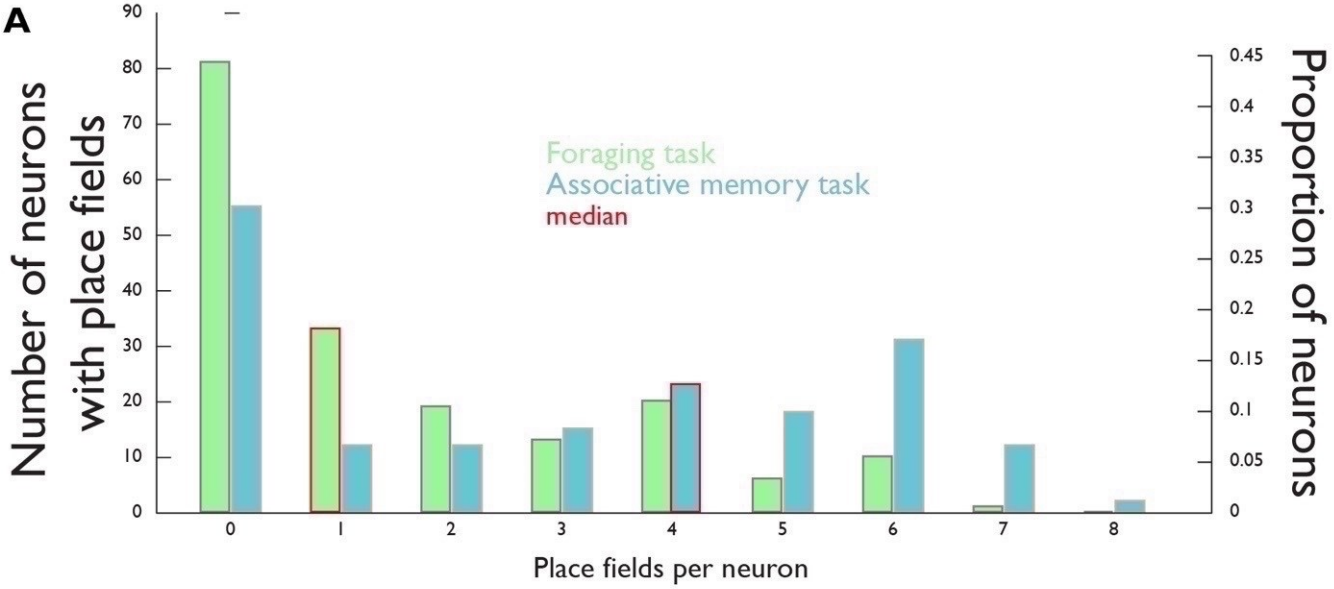
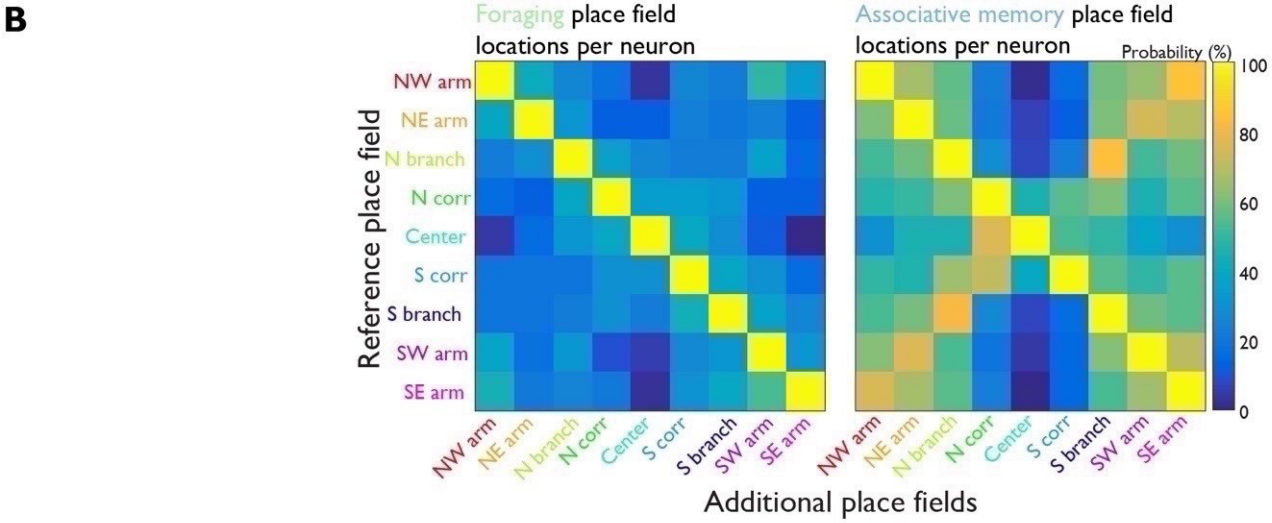


Figure 3.3. Single neuron place fields in each task

Number of neurons with significant firing rates in each pixel and each area of the maze in the foraging and associative memory tasks.

*$p<0.05$, χ^2 test of equal proportions within maze areas, across tasks


A
Number of neurons with place fields
Proportion of neurons
Foraging task
Associative memory task
median
Place fields per neuron


B
Foraging place field locations per neuron
Associative memory place field locations per neuron
Probability (%)
Reference place field
NW arm
NE arm
N branch
N corr
Center
S corr
S branch
SW arm
SE arm
Additional place fields

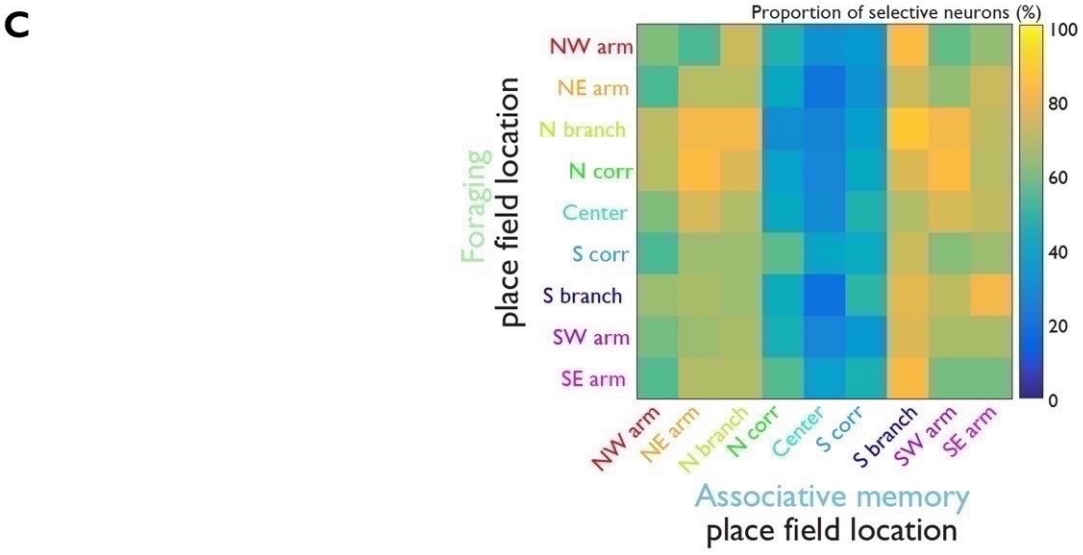

C
Proportion of selective neurons (%)
Foraging place field location
Associative memory place field location

Figure 3.4. Number and distribution of place fields per neuron across tasks

(previous page)

A) Number of place fields per neuron in each task

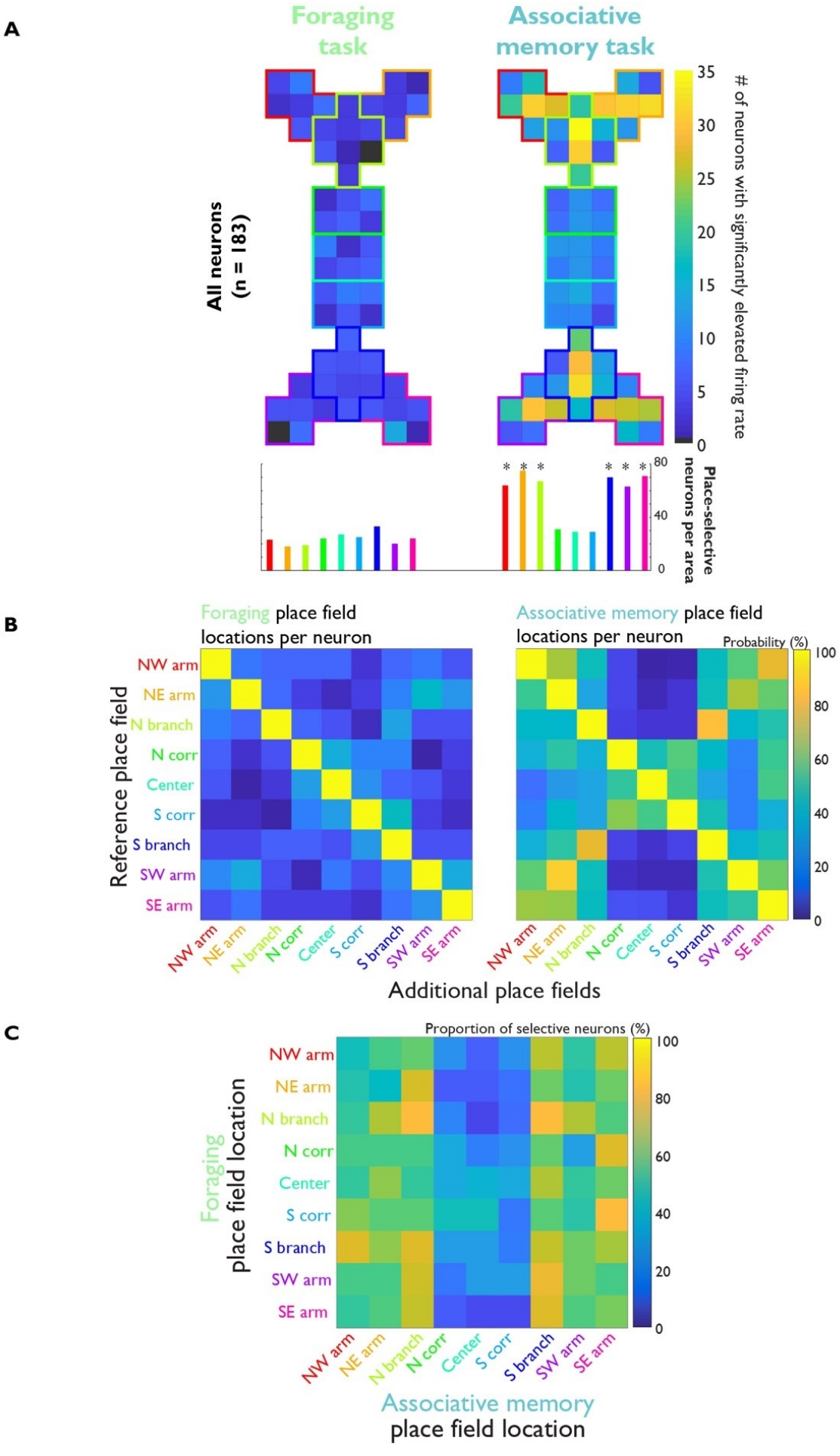
B) Locations of coincident place fields for all neurons with more than one place field in each task

C) Location of coincident place fields for all neurons with at least one place field in each task

Figure 3.5. The effect of pixel size on single neuron place fields in each task

(next page)

Conventions are the same as in **Figure 3.3** and **Figure 3.4**. However, all visualizations and statistics have been done with pixels that are 4 times larger than those in the previous figures.


A
Foraging task
Associative memory task
All neurons (n = 183)
# of neurons with significantly elevated firing rate
35
30
25
20
15
10
5
0
Place-selective neurons per area
80
40
0
B
Foraging place field locations per neuron
Associative memory place field locations per neuron
Probability (%)
100
80
60
40
20
0
Reference place field
NW arm
NE arm
N branch
N corr
Center
S corr
S branch
SW arm
SE arm
Additional place fields
C
Proportion of selective neurons (%)
Foraging place field location
Associative memory place field location

3.3.2 Single neuron spatial information content varies across tasks

An additional measure of spatial encoding in individual neurons was used to quantify firing specificity in each task; spatial information content (SIC) quantifies how many bits of information about the location of the subject are transmitted per action potential (Markus et al., 1994; Ravassard et al., 2013; Skaggs et al., 1993). Empirical and circularly shuffled control SIC values were computed using occupancy vectors and firing rate vectors, much the same as previously described (see **Section 3.2.3**). **Figure 3.6** shows the number of neurons with SIC values that exceed the statistical threshold for significance compared to the null distribution of each pixel (alpha=0.05/number of occupied pixels). This provides a two-dimensional depiction of the number of neurons in each pixel that contain more information than would be expected by chance.

In the foraging task, 27.3% of neurons had significant SIC summed over the entire spatial map. The location of pixels with significant SIC were homogeneously distributed throughout the maze ($p=0.59$, $\chi^2(8) = 6.56$; **Figure 3.6**, left column). In the associative memory task, 67.2% of neurons showed significant SIC. The location of pixels with significant SIC were not homogeneously distributed throughout the maze ($p=0.0004$, $\chi^2(8) = 28.5$; **Figure 3.6**, right column), and the proportion of neurons with significant SIC during the associative memory task exceeded that observed in the foraging task for all maze areas (McNemar's test for equal proportions; p-value range $0.005 - 1\times10^{-7}$). Though more neurons exhibited significant SIC in the associative memory task than the foraging task, the distribution of empirical SIC values was not different between tasks (**Figure 3.6**; two-sample Kolmogorov Smirnoff test, $p=0.66$).

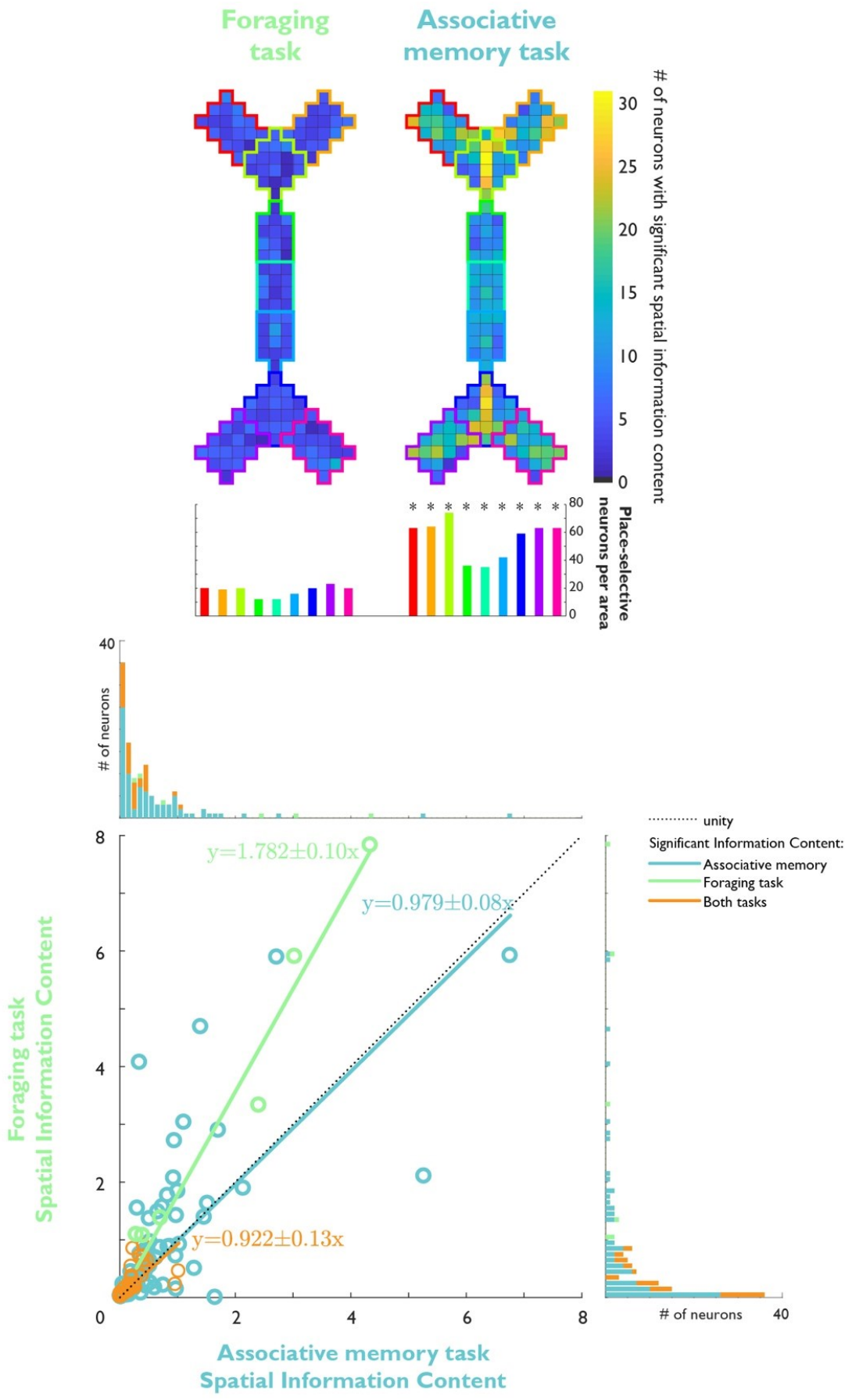

Foraging task
Associative memory task
# of neurons with significant spatial information content
30
25
20
15
10
5
0
Place-selective neurons per area
80
60
40
20
0
# of neurons
40
unity
Significant Information Content:
Associative memory
Foraging task
Both tasks
y=1.782±0.10x
y=0.979±0.08x
y=0.922±0.13x
Foraging task
Spatial Information Content
Associative memory task
Spatial Information Content
0
2
4
6
8
# of neurons
40

Figure 3.6. Spatial Information Content in both tasks

(previous page)

A) Spatial histogram showing the number of neurons with statistically elevated spatial information content in each pixel in both tasks (top). The summarized histogram (bottom) shows the number of neurons with at least one significant pixel in each maze area. *significantly different proportion across tasks; McNemar's test of equal proportions, $p<0.05$, Bonferroni-corrected

B) Histogram and scatterplot of significant spatial information content values in each task. Only neurons with empirical spatial information values above the 95th percentile of circularly shifted permutation test values are included. Inset: Cumulative distribution of spatial information content in each task

3.3.3 Spatial position can be decoded from population activity

The previous results show that individual neurons contain information about space in each task, but statistical descriptions of selectivity in single neurons may not be sufficient in capturing the wealth of information encoded by neural populations (Fusi et al., 2016; Rigotti et al., 2013). The stability of a holistic population code for space and the optimal spatial reference frame cannot be assessed in single neurons. Therefore, the firing rates from the entire population of neurons were used to decode subject position in the maze within and across tasks, and using allocentric and direction-dependent spatial reference frames (**Figure 3.7 A**).

We used a multi-class support vector machine with a linear kernel to decode the subject's position in space using neuronal firing rates (Fan et al., 2008); **Section 3.2.4**). Briefly, an ensemble was constructed using firing rates from each neuron in 10 passes through each maze area for each task; neurons with less than 10 trials in any condition were excluded (n=152 neurons included). Decoding accuracy was tested using cross-validation. The ensemble was stratified into 5 folds, with 4 of these used for parameter normalization and model training, and the remaining fold used for model testing. A null distribution of decoding accuracies was derived by permuting the labels of the testing fold. This procedure was repeated 100 times, yielding distributions of empirical (**Figure 3.7 B**, colour distributions) and null (**Figure 3.7 B**, grey distributions) decoding accuracy. Statistical differences between accuracy distributions were assessed via Wilcoxon ranksum.

The classifier predicted position in the maze above chance levels in both tasks when using an allocentric spatial reference frame (**Figure 3.7 B**, first and second column; foraging: 1.50±0.45 times permuted control (mean ± standard deviation; p<10-12; associative memory: 2.22±0.53 times permuted control; $p<10^{-31}$). However, accuracy was poor (foraging task Cohen's κ=0.06; associative memory task Cohen's κ=0.15; **Section 3.2.5**). The classifier systematically confounded structurally similar areas of the maze in both tasks, as evidenced by the X-shaped distribution of predictions in the allocentric decoder confusion matrices (**Figure 3.7 C**).

Decoding position using an idiothetic, direction-dependent reference frame, prediction accuracy was 1.71±0.39 (p=0.09 compared to allocentric; **Figure 3.7**; third column). In the associative memory task, decoding accuracy improved to 3.01±0.48 (p<10-10 compared to allocentric; **Figure 3.7 B**, fourth column). These results indicate that populations of hippocampal neurons encode spatial position more reliably in a direction-dependent idiothetic reference frame, consistent with previous findings across species (Acharya et al., 2016).

It is possible that a small subset of the population that fires with high spatial specificity drives the decoding accuracy in these analyses. This was tested directly using a drop-out procedure, in which the decoding analyses were repeated, progressively excluding the neuron the highest SIC until the population dwindled to a single neuron. When dropping neurons based on SIC, the partial population decoding accuracy drops below the accuracy of the whole population accuracy at a population size of 14 neurons (**Figure 3.8**). Thus, this shows evidence that the ensemble decoding results shown in **Figure 3.7** are not attributed to few, highly-spatially specific neurons.

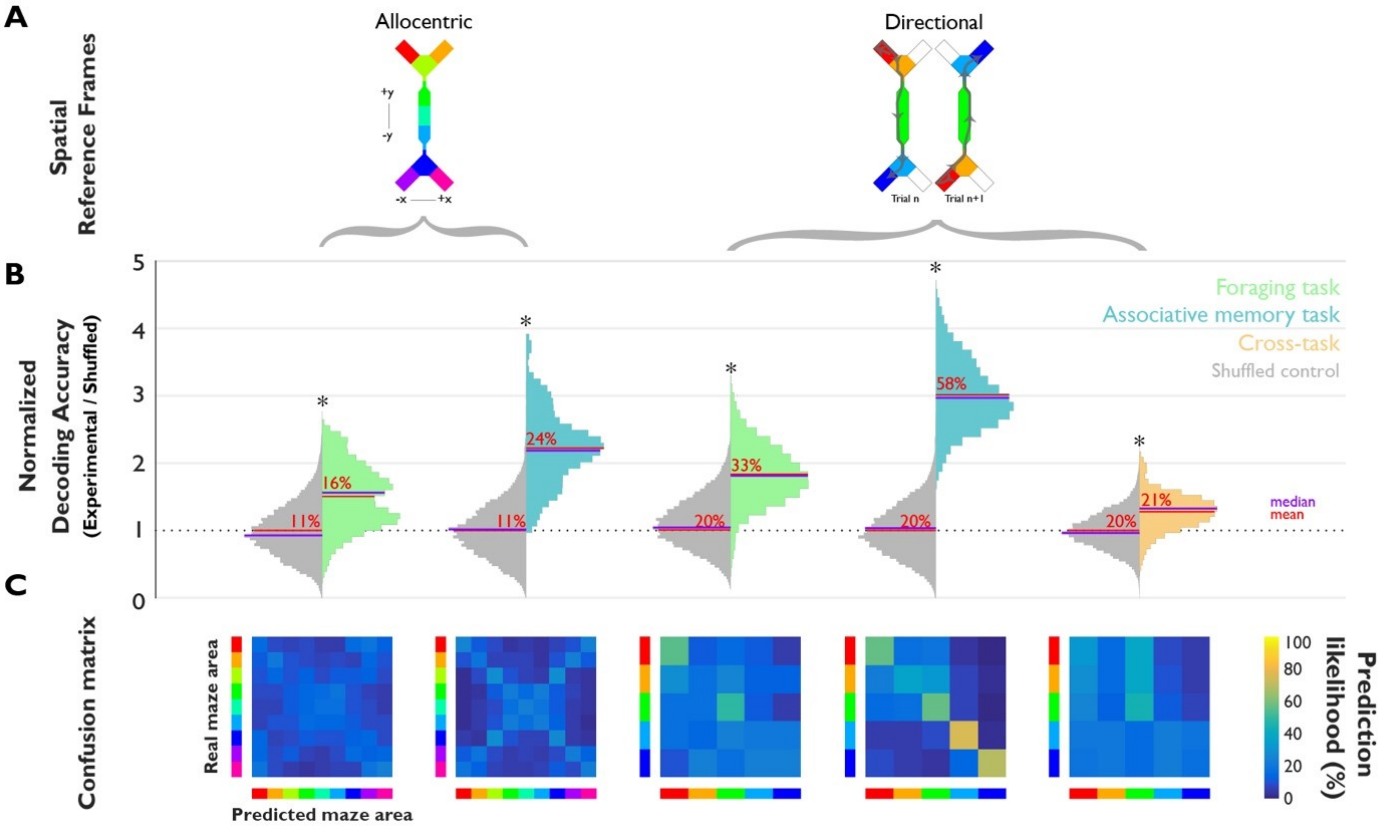


Figure 3.7. Hippocampal ensemble prediction of spatial position with a linear classifier

A) Spatial reference frames used in each of the lower panels of spatial classification analyses

B) Distributions of classification accuracies for spatial position in the foraging (green) and associative memory (blue) tasks as well as cross-task testing and validation (orange). *p<0.05 real vs. shuffled distribution (grey distributions), Wilcoxon ranksum.

Red bars and numbers, mean; purple bars, median

C) Confusion matrices for each classification analysis. Real location=rows; predicted location=columns; colour map, prediction likelihood

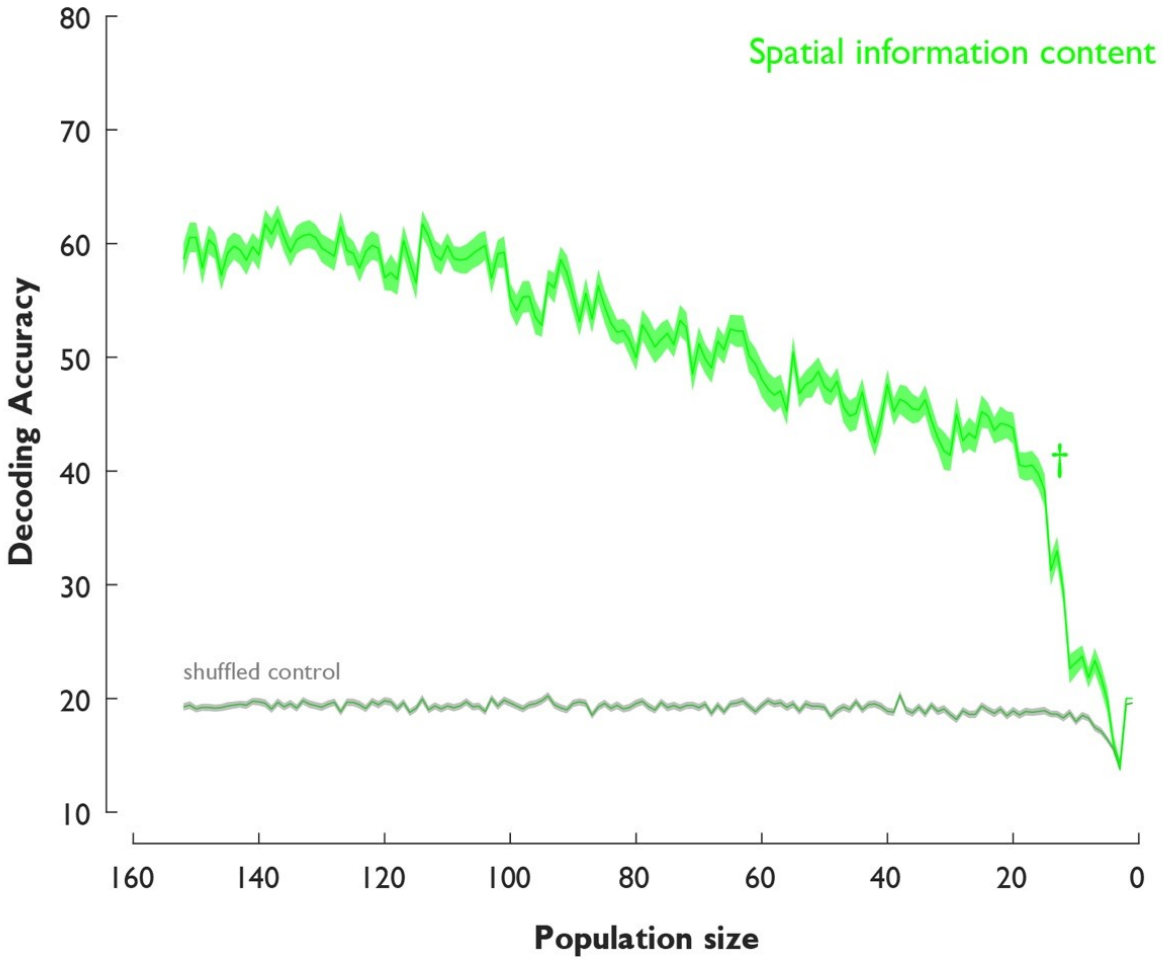


Figure 3.8. Robustness of direction-dependent decoding in the associative memory task to neuron drop-out

Spatial decoding accuracy when the population of neurons is progressively diminished on the basis of individual neuron spatial information content.

†, decoding accuracy 2 standard deviations below decoding accuracy for the entire population of neurons

3.3.4 Cross-task comparison of population models of spatial position

Though subjects' position in space could be decoded from the population of neurons in each task, it is not clear whether coding of space generalized across tasks; that is, whether an abstract representation exists, invariant to the task that the animal is engaged in (Saez et al., 2015). To determine whether the cognitive map of space generalized across tasks, a linear support vector machine was trained using trials from the foraging task and tested using trials from the associative memory task. Classification accuracy when training and testing across tasks fell below accuracy in the foraging and associative memory task (**Figure 3.7**, $p<10^{-5}$ and $p<10^{-17}$, respectively). Results were unchanged when the training and testing sets were swapped. This indicates that coding of spatial position by the ensemble of recorded neurons does not generalize across tasks and suggests that the spatial information carried by the population of recorded neurons changes across tasks.

The poor abstraction of spatial representation across tasks could be due to a global change across the entire X-Maze, or differences in parts of the maze where behavioural demands differed across tasks (branches and arms). At these points, object- and context-driven comparison and selection of targets is required only in the associative memory task. On the other hand, cue guided navigation through the central corridor was a common requirement across tasks. Across different areas of the maze, the prediction accuracies are not uniform ($p<10^{-5}$, Kruskal-Wallis), with the highest decoding accuracy found in the corridor of the X-Maze, suggesting that the population code for space across tasks is most similar in this area of the maze. This was further corroborated by correlating the weights assigned to each neuron by the linear classifier in the corridor, arms and branches across tasks (**Figure 3.9**). Indeed, individual neuron contribution to direction-dependent position classification was most similar in the central corridor and the portion of the maze leading into the corridor (**Figure 3.9**; "Branch to corridor", orange, regression slope 0.34, 95% CI 0.21-0.47, $R^2=0.15$, $p<10^{-5}$; "Corridor", green, regression slope 0.46, 95% CI 0.29-0.62, $R^2=0.16$, $p<10^{-6}$). On the other hand, each neuron's contribution to the ensemble code in the arms and branches of the maze were not preserved across tasks (**Figure 3.9**, "Arms to branch", red, $R^2=0.02$, $p=0.08$; "Branch to arm", light blue, $R^2=0.01$, $p=0.14$; arm towards end, dark blue, $R^2=0.00$, $p=0.92$). Thus, the spatial code of the neuronal population is preserved when task demands and the environment are similar, but changes where novel features are introduced and new task relevant behaviour is required.

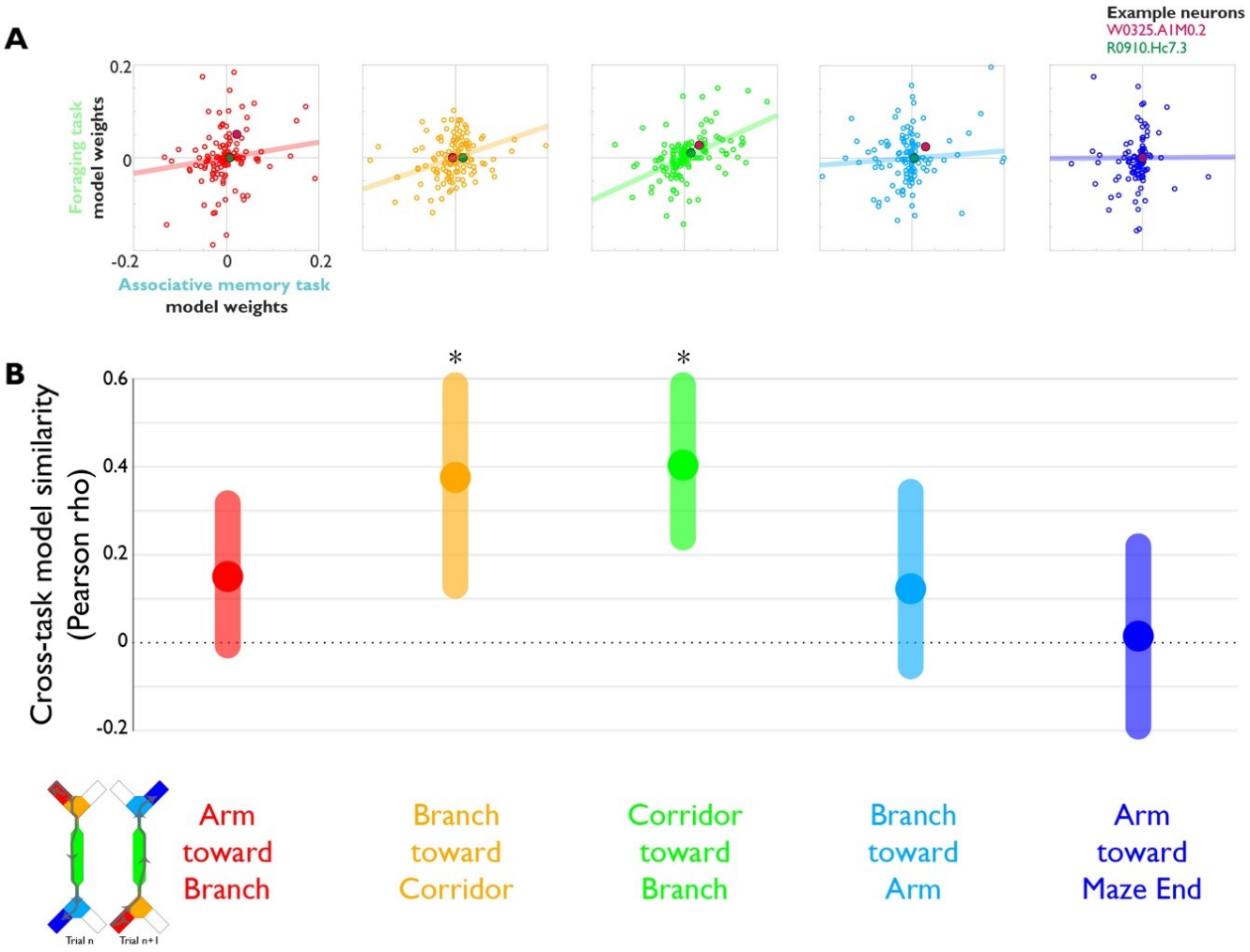


Figure 3.9. Cross-task comparison of individual neuron contribution to the population model of direction-dependent spatial position

A) Scatterplot of each neuron's model weight for each area of the maze across tasks. Shaded line, correlation slope

B) Pearson correlation coefficient of decoding model weights for each neuron between the foraging and associative memory task. Circle, median; shaded bars, 99% confidence interval; *p<0.01

4 Non-spatial Information in the Hippocampus

"'But the great difficultly is this,' interrupted the Psychologist. 'You can move about in Space, but you cannot move about in Time.'

'That is the germ of my discovery. But you are wrong to say that we cannot move about in time. For instance, if I am recalling an incident very vividly I go back to the instant of its occurrence: I become absent-minded, as you say. I jump back for a moment. Of course we have no means of staying back for any length of Time, any more than a savage or an animal has of staying six feet above the ground.'"

H.G. Wells, The Time Machine, pg 4

4.1 Synopsis

In Chapter 3: Spatial Information in the Hippocampus consilient evidence suggests that neurons recorded in the non-human primate hippocampus do not provide a task-invariant, generalizable code for space. Evidence for this is strongest in areas of the maze where the behavioural demands of the associative memory task are most stringent. The question of what mediates the differences in hippocampal neuronal activity across tasks remains.

In this chapter, neuronal activity is analysed in each period of the associative memory task with respect to the trial-varying features of the task. This is done for sensory features — those currently in the environment — and memory for those features after they are no longer present in the virtual environment.

Encoding and decoding models showed that trial context, objects, and their conjunction were encoded in individual neurons as sensory and mnemonic representations. Sensory and mnemonic encoding was observed in largely disparate populations of neurons. The population of neurons could be used to reliably predict the identity of trial-varying features in sensory and memory periods of the task. Finally, when spatial decoding procedures from the previous chapter were repeated with a population of neurons that diminished on the basis of trial feature encoding, the spatial decoding accuracy dropped faster than when the "most spatial" neurons were removed.

These results show that non-spatial trial-varying features are encoded in hippocampal neurons in each trial period of the associative memory task. Furthermore, these neurons are consequential to the previously observed spatial encoding. In these analyses though, the examined parameters of the task are reduced since firing rates are integrated over long periods of time (seconds). Given that the hippocampus is believed to be critical for learning relationships between behaviourally-relevant objects in the environment, an examination of firing rate as a function of overt attention and learning behaviour should also be conducted.

4.2 Methodology

4.2.1 Non-spatial feature selectivity

For two example neurons, changes in firing rate in each trial period were examined as a function of non-spatial trial features (chosen object colour, trial context, and their

conjunction) from the current and previous trial (**Figure 4.2 A** and **B**). Key trial events delineated trial periods. The post-reward period and pre-context period were equally split intervals of time between the start of the current trial (~200ms after reward from the previous trial ended) and the first frame where the context material was applied to the walls of the central corridor. The context appearance period started at this frame and extended for the entire path of the subject through the corridor. Upon reaching the end of the corridor, the subject's view in the maze was gently corrected to face cardinal direction north or south precisely, and subsequently both objects were triggered to appear simultaneously in the ends of the maze. The frame where the objects were first visible marked the end of the context appearance period, and the start of the decision period (object appearance). The subjects were free to take as long as needed to decide to navigate to the left or right object. The first frame at which the subject's orientation deviated from the cardinal North or South direction, as part of a rotation that eventually exceeded 10° of deviation from the midline marked the end of the decision period, and the start of the goal reward period. The object approach period ended when the subject first touched the chosen object for that trial. Note, the next trial's post-reward period started approximately 200ms after the end of the reward delivery.

We used multiple linear regression to determine whether each neuron's firing rate was modulated as a function of non-spatial trial features (i.e., trial context, trial object colour, and their conjunction) in each trial period of the associative memory task. This procedure was repeated using trial features for the current and previous trial. Formally,

$$y_{ij} = \beta_{0ij} + \beta_{1ij}x_{1ij} + \beta_{2ij}x_{2ij} + \beta_{3ij}x_{3ij} + \varepsilon_{ij}$$

where y describes the change in a neuron's firing rate within each task period (i; 1, post-reward period; 2, pre-context; 3, context appearance; 4, decision; 5, object approach) for current and previous trial features (j; 1, current trial features; 2, previous trial features). Fit parameter (β_0) describes the intercept of the regression line. ε estimates the residual. β_1, β_2, and β_3 describe the effect of chosen object, trial context, and their conjunction, respectively. Statistical significance of each of these parameters was assessed using a partial F-test, wherein the error of the full model is compared to that of a model with one parameter omitted. The proportion of all neurons (n=183) with significant fit parameters for object, context or their interaction is reported in **Figure 4.2 C**.

4.2.2 Sensory versus Mnemonic Trial Feature Encoding

The F-statistic of the fit parameters β_1, β_2, and β_3 were used to compare sensory and mnemonic encoding of associative memory trial features in individual neurons. Specifically, **Figure 4.3 A** shows the scatterplot of neurons' regression coefficient during the goal approach period (sensory encoding) versus the post-reward period (memory encoding).

The proportion of neurons with significant regression coefficients for each parameter was compared using McNemar's test of proportions (**Figure 4.3 A**, insets).

The relationship between sensory and memory encoding for each trial parameter for each neuron was characterized using the Pearson correlation coefficient rho (**Figure 4.3 B**). Rho was calculated over 10,000 bootstrap iterations, and **Figure 4.3 B** shows the median and 96.7% confidence interval (alpha = 0.05/number of trial parameters).

4.2.3 Trial Type Classification

Trial type classification (**Figure 4.4**) was done using Glmnet (Friedman et al., 2010) using firing rates from all neurons included in the spatial decoding analyses (n=152). For the Sensory condition, each neuron's firing rate in each from the Corridor, Goal appearance and Goal approach periods were included as predictors. For the Memory condition, firing rates from the Post-reward and Pre-context periods were used as predictors. In the Sensory+Memory condition, all 5 periods were used. Because of the high ratio of model predictors to training and testing examples for these analyses, Glmnet classification was used with elastic net regularization. A nested cross-validation procedure was used to appropriately tune model hyperparameters (regularization parameter lambda, and elastic net L1-L2 weighting parameter alpha, via grid-search) and test on hold-out sets of trials never seen by the trained model.

4.3 Results

4.3.1 Individual neurons encode sensory and mnemonic features of the associative memory task

The previous results show where in the X-Maze the population code for space changes, but not which parameters of the task are being encoded in each area. Changes in the population model for each maze area across tasks may be due to neurons encoding features of

the associative memory task (context, object colour, and their conjunction) that are relevant in these areas of the maze. To examine this encoding, each trial was split into five periods closely corresponding to the five areas of the maze used in the direction-dependent spatial decoding (Post-reward, Pre-context, Context appearance, Decision, Object approach; see **Figure 4.2**). Firing rate was regressed for each neuron against the trial-varying parameters of the associative memory task in each period. This was done using the context and object of a given trial and the firing rate in each period of the same trial (sensory encoding; **Figure 4.2**, left plots), or the firing rate in each period of the next trial (memory encoding; **Figure 4.2**, right plots).

One example neuron shown in **Figure 4.2 A** fired most in the arms of the maze. Plotted as a function of trial period in the associative memory task, this neuron fires immediately after the reward was delivered; post-reward firing was not observed in the foraging task (**Figure 4.1**). This example neuron was selective for previous trial features during the post-reward period (**Figure 4.2 A**); firing rate was highest following trials where the lowest value object was chosen, and no reward was delivered ($p<10^{-4}$, Kruskal Wallis). This encoding cannot be explained by sensory features such as object colour, context or reward size alone; but only by the conjunction of these features, even though none of these features were visible during the post-reward period.

Another example neuron shown in **Figure 4.2 B** fired exclusively between the subject's initial turn towards the chosen object and the moment of first contact (goal approach period; **Figure 4.1**). This neuron was most active during approaches to a single object colour regardless of context, and did not fire when approaching an intermediate value object (**Figure 4.2 B**; p<10-20, Kruskal Wallis).

On a population level, a diverse array of selectivity for associative memory trial features was observed. The chosen object colour was most robustly encoded during the object approach (46/183 neurons, 25.14%; **Figure 4.2 C**, left, yellow dots). The conjunction of object and context of the previous trial was encoded by the same number of neurons during the post-reward period (**Figure 4.2 C**, right, yellow dots with blue outline). Encoding of trial context peaked in the corridor of the maze (sensory: 16/183 neurons, 8.7%, memory: 18/183 neurons, 9.8%; **Figure 4.2 C**, blue dots).

These results show non-spatial sensory and mnemonic encoding changes across trial periods of the associative memory task. It is not known whether these functions are supported

by a common or separate population of hippocampal neurons. To compare sensory and memory encoding of each neuron for each trial parameter, F-statistics from each neuron's encoding model during goal approach (sensory) and post-reward (memory) periods were correlated (**Figure 4.3**). Similar proportions of neurons showed prospective and retrospective coding of contexts (**Figure 4.3 A**, left, p=0.68, McNemar's test of equal proportions) or objects (**Figure 4.3 A**, middle, p=0.12, McNemar's test of equal proportions). However, for the combination of object and context, the proportion of neurons showing memory coding was significantly larger than sensory coding (**Figure 4.3**, left, p=0.0005, McNemar's test of proportions). The strength of sensory versus memory coding in individual neurons was not correlated for trial context (**Figure 4.3 B**, Spearman rho 95% confidence interval = -0.12–0.25); in contrast, sensory and memory coding for objects and combinations of contexts and objects were correlated (**Figure 4.3 B** objects: Spearman rho 95% confidence interval = 0.13–0.48; context×object: 0.05–0.40).

Figure 4.1. Example neuron rewarded-aligned spike rasters

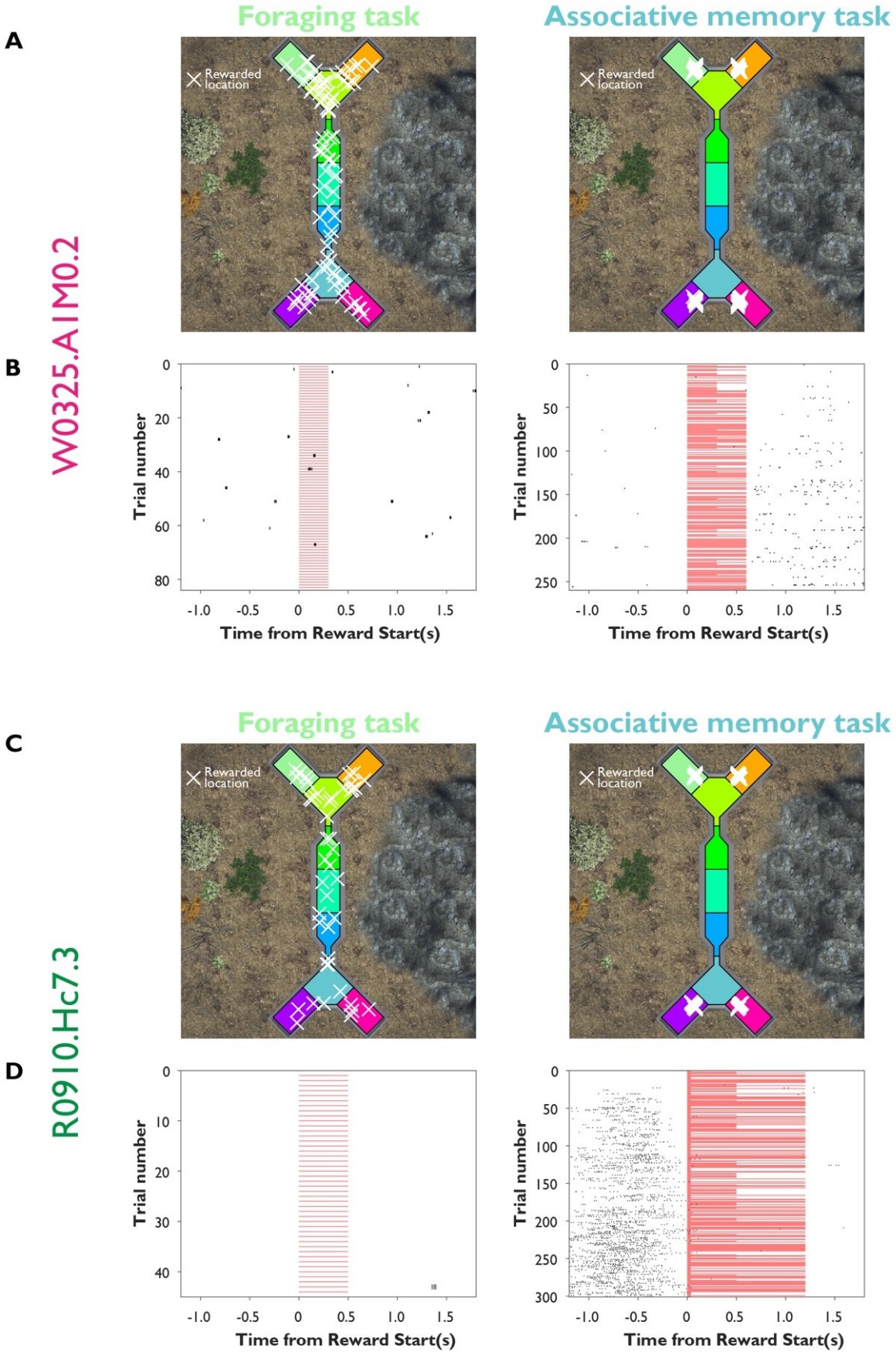
(next page)

A) Monkey position in the X-Maze for all reward deliveries in each task during session W0325

B) Reward-aligned rasters show an increase in firing only after reward delivery in the associative memory task.

C) Conventions as above for session R0910

D) Conventions as above, with highest firing rates occurring prior to reward delivery


A
Foraging task
Associative memory task
Rewarded location
W0325.A1M0.2
B
Trial number
Time from Reward Start(s)
C
Foraging task
Associative memory task
Rewarded location
R0910.Hc7.3
D
Trial number
Time from Reward Start(s)

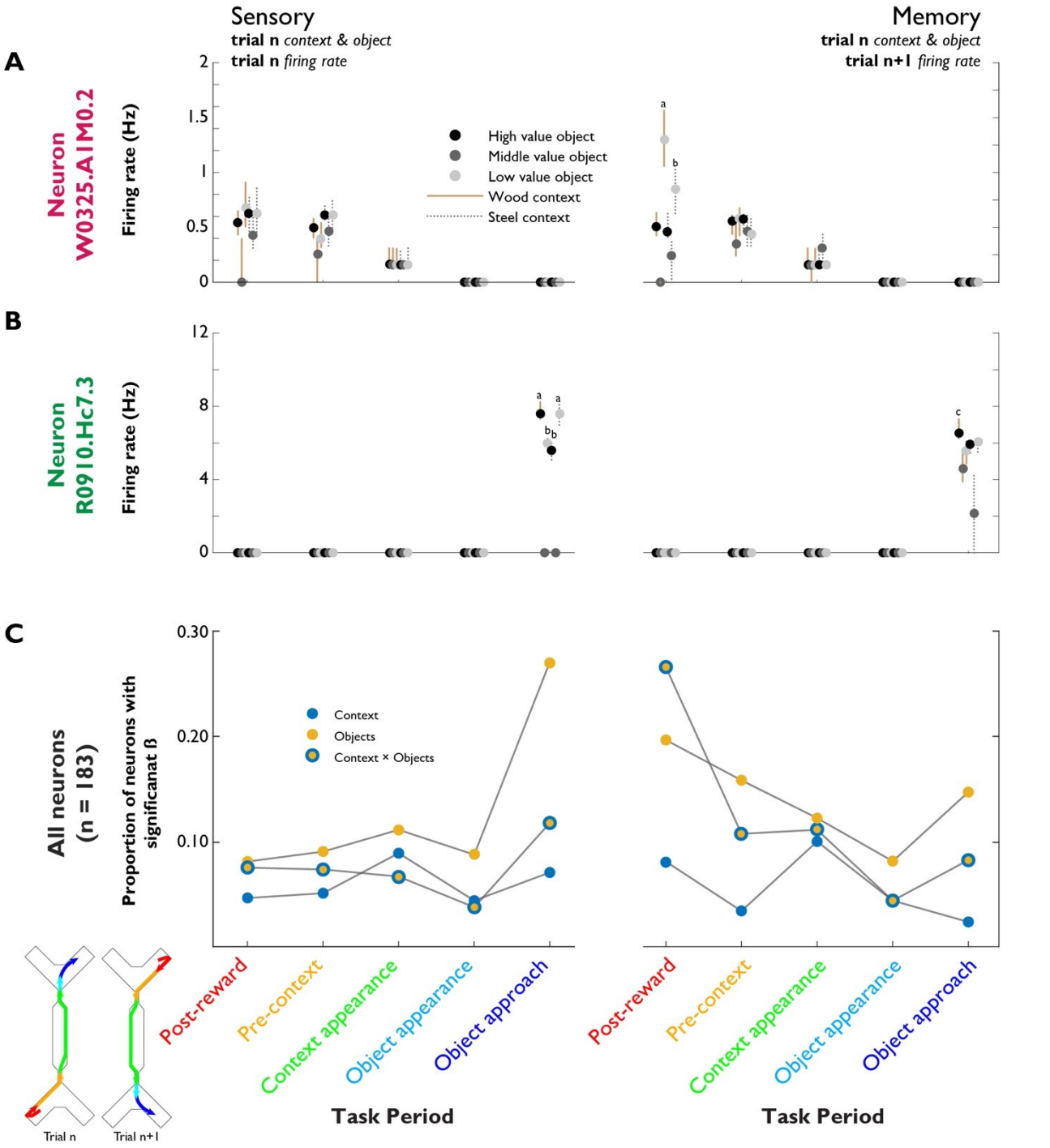


Figure 4.2. Non-spatial feature selectivity in the associative memory task

Selectivity of each neuron for non-spatial features of the associative memory task. Selectivity is computed using trial parameters of trial n and firing rates from the same trial (sensory; left plots), or trial n+1 (memory; right plots).

A) Example neuron W0325.A1M0.2. an object-value selective neuron. Letters denote categories with significantly different firing rates within that condition ($p<0.05$, Bonferroni adjusted)

B) Example neuron R0910.Hc7.3, an object-colour selective neuron. Conventions as in (A)

C) Proportion of single neurons selective for non-spatial associative memory task features: context (blue dot), chosen object colour (yellow dot), and the combination of these two (yellow dot, blue outline)

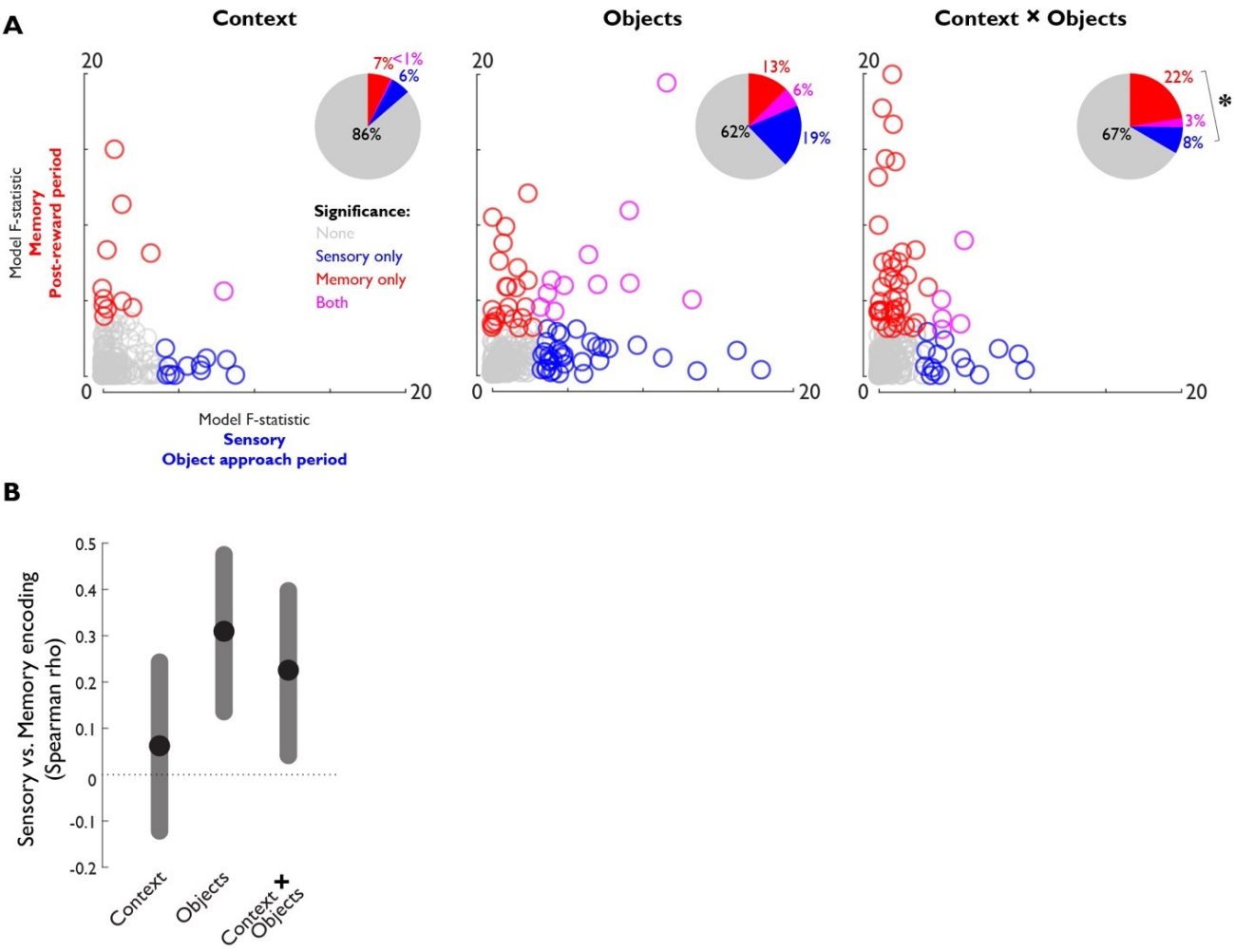


Figure 4.3. Sensory versus Memory encoding of trial features

A) Sensory versus memory encoding model: fit parameter F-statistic comparison. Inset: percentage of neurons with significant fit parameters for each encoding model

B) Spearman correlation coefficient of encoding model F-statistics for each neuron between the foraging and associative memory task. Circle, median; shaded bars, 99% confidence interval

4.3.2 Associative memory trial type is encoded by the population

We used a linear classifier to determine the accuracy with which the population of hippocampal neurons can predict the context and object pair of a given trial (associative memory trial type). One classifier was trained to predict context and object of the current trial from three sensory trial periods (context appearance, decision, and object approach; **Figure 4.4**, Sensory); another was trained using two memory trial periods (post-reward and pre-context; **Figure 4.4**, Memory). In both classifiers, each neuron's firing rate in each trial period was used as an independent predictor. A logistic classifier with elastic net regularization was used to avoid problems of overfitting associated with having many predictors and a limited number of model training examples (Friedman et al., 2010).

Using only the sensory or memory trial periods, prediction accuracy was above chance (sensory: 2.88±1.13 times permuted control; $p<10\text{-}86$, Wilcoxon ranksum, Cohen's $\kappa=0.24$; memory: 2.04±0.95; $p<10\text{-}58$ times permuted control, Wilcoxon rank-sum, Cohen's $\kappa=0.12$). Using the firing rates from both the sensory and memory trial periods in a single classifier, classification accuracy further increased (3.29±1.12 times permuted control; $p<10\text{-}97$, Wilcoxon ranksum; Cohen's $\kappa=0.31$).

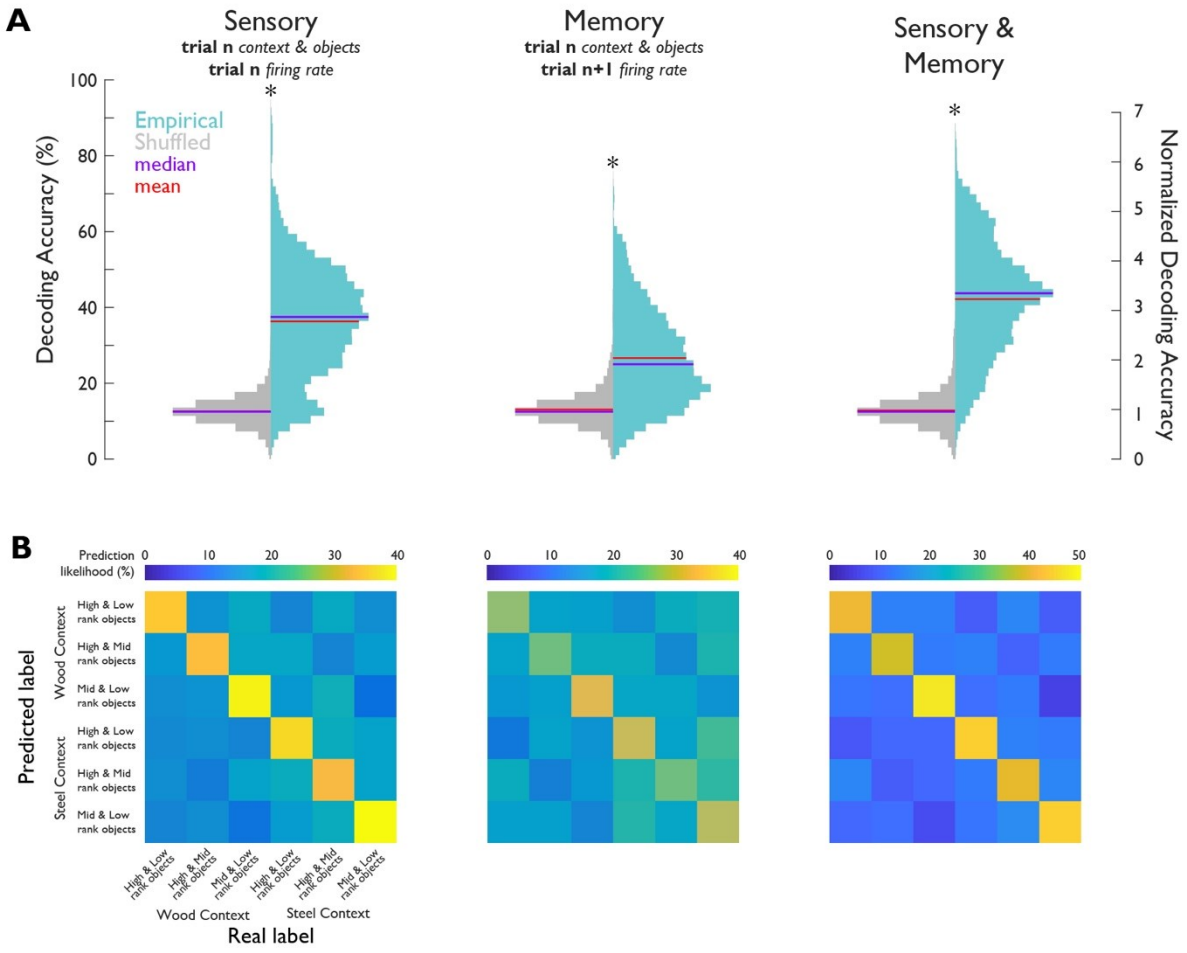


Figure 4.4. Trial type decoding in the associative memory task

(A) Distribution of classification accuracies from decoding analysis of trial type (trial context and object pair) in the associative memory task.

*p<0.05 real vs. shuffled distribution (grey distributions), Wilcoxon ranksum.

Red bars, mean; purple bars, median

(B) Confusion matrix derived from the classification analysis. Predicted trial type=rows; real trial type=columns; colormap, prediction likelihood

4.3.3 Sensitivity of spatial coding to drop-out of trial-feature encoding neurons

Thus far, these results have shown that individual neurons encode trial-varying features of the associative memory task differently across trial periods of the task. Furthermore, the population activity in sensory and memory trial periods can used to decode the trial-varying features of the task. These trial periods are closely related to the areas of the maze defined in the direction-dependent spatial decoding shown in **Figure 3.7**, which was shown to robust to drop-out of neurons with high spatial information content in **Figure 3.8**. Since spatial selectivity could be confounded or conjunctively represented with trial feature selectivity, a logical extension to previous analyses would be to test the robustness of spatial decoding when neurons were dropped out based on their selectivity for trial-varying parameters of the associative memory task. Thus, starting with the original population, neurons were progressively removed based on their summed F-statistics derived from each parameter of the multiple linear regression models examined in **Section 4.3.1**.

When dropping neurons based on summed F-statistic from the associative memory task regressions (**Figure 4.5**, blue line), decoding accuracy calls two standard deviations below the whole population accuracy at a population size of 30 neurons (marked with blue † above). Using an alternative method to find the most significant change point in the mean decoding accuracy, the most significant inflection point in the dropout curve occurs at a population size of 27 neurons.

The sensitivity to neuron drop-out on the basis of trial-feature encoding (**Figure 4.5**, blue line) and spatial information content (**Figure 4.5**, green line, reproduced from **Figure 3.8**) was compared at each population size using a Wilcoxon ranksum test. Due to the large number of comparisons, significance was assessed using a label permutation procedure. The labels of the accuracy distributions from both drop-out methods were shuffled, and the statistical test was repeated to create a distribution of null p-values. In all cases where statistical differences between population decoding accuracies were identified, the population decoding accuracy was more sensitive to drop-out based on trial-feature encoding. Each ensemble size where the empirical p-value is lower than the 5^{th} percentile of p-values from the null distribution of p-values is marked with an asterisk in **Figure 4.5**.

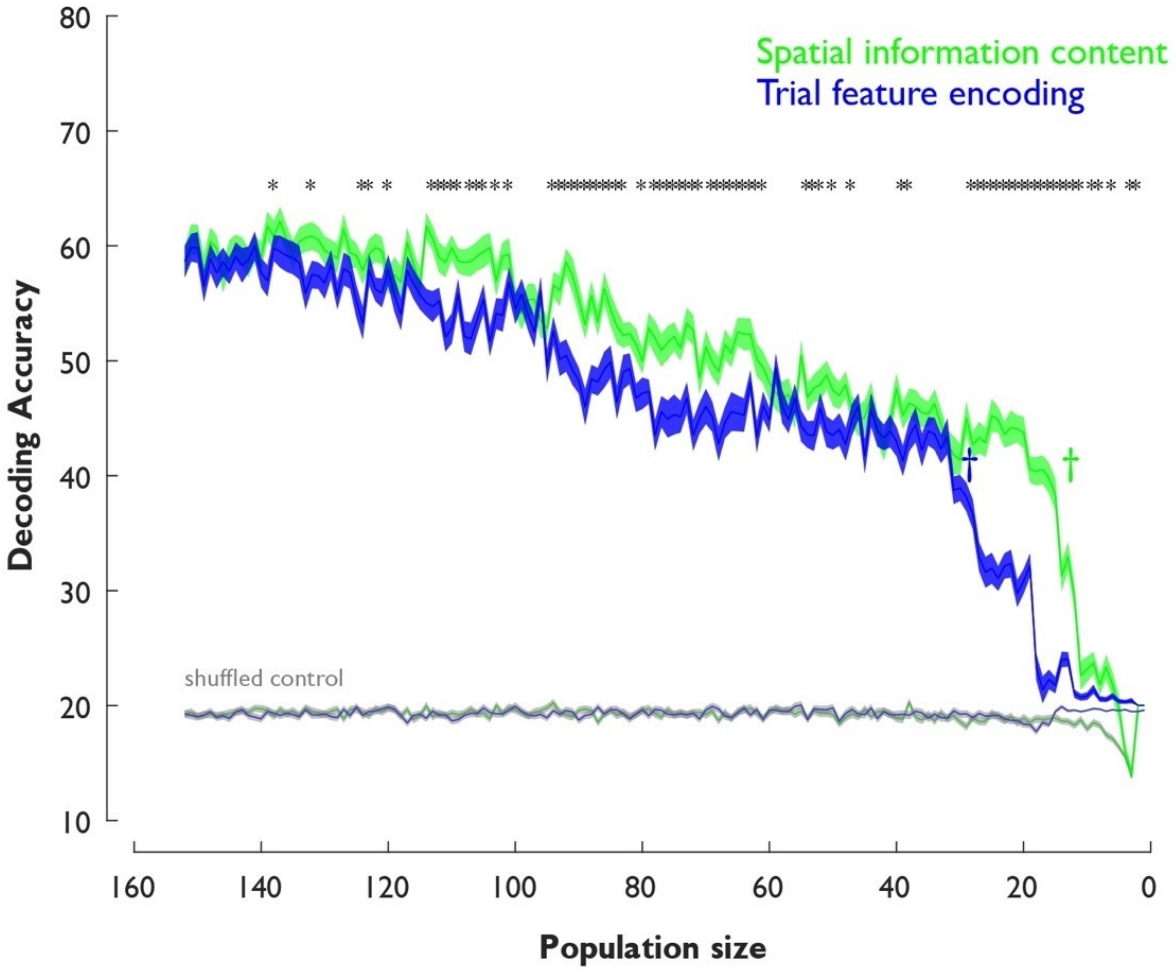


Figure 4.5. Spatial decoding with trial-feature encoding neuron drop-out

Spatial decoding accuracy when the population of neurons is progressively diminished on the basis of individual neuron spatial information content (green line) or summed F-statistics of encoding models for trial-varying parameters (blue line).

†, decoding accuracy 2 standard deviations below decoding accuracy for the entire population of neurons

*, significant difference between decoding accuracy for a given population size; $p<0.05$, Wilcoxon ranksum

5 Representation of Foveated Objects and Changes with Learning

"It has been sagaciously discerned by Simonides… that the keenest of all our senses is the sense of sight, and that consequently perceptions received by the ears or by reflexion can most easily be retained if they are also conveyed to our minds by the mediation of the eyes."

De oratore, II, lxxxvii, 357.

5.1 Synopsis

The previous chapters have shown that spatial responses observed in monkey hippocampal neurons are task-dependent, and can be attributed to sensory and mnemonic representations of trial-varying features of a behavioural task.

In this chapter, neural activity is examined in the associative memory task as a function of the best available proxy for subject's overt attention. That is, neural activity is analysed with respect to the specific objects in the environment that are being foveated.

For every foveation that occurred during the associative memory task, the gaze projection in the virtual environment was used to retrieve the identity of each foveated object. Using multiple metrics, it is shown that hippocampal neurons encode information about which object was being foveated, and a proportion of neurons are selectively active during foveations to each object in the environment.

Associative memory task performance was not a fixed variable; this performance variability allows for the examination of object selectivity as a function of learning state. Across learned and unlearned associations, the proportion of neurons that encode information about foveated objects was similar, as was the amount of information. Within associations, selectivity in a subset of neurons was correlated with learning state.

These results show that it is not only objects that are relevant to the associative memory task that seem to be encoded by monkey hippocampal neurons. These results have broad implications for neuropsychological and computational theories of hippocampal function.

5.2 Methodology

5.2.1 Gaze analyses

As described in **Section 2.2,** player position in the virtual environment was sampled every frame, and eye position on the screen was recorded at 500Hz. Since the instantaneous player and eye-on-screen positions were both known, it was possible to reconstruct gaze position in the environment using ray tracing.

For every recorded eye position, the vector from the subject to the eye-on-screen position was computed. Offline, a ray was cast along this vector in the virtual environment using custom-built scripts in Matlab and Unreal Engine, until it intersected with a virtual

object (**Figure 5.1**), returning the identity of the object at the foveated position. Eight more ray vectors were cast around the central vector, to provide 9 total objects intersections that spanned approximately 3° of visual angle on the screen. These object identities within the foveal region were recorded for each time point. Furthermore, the centre of the gaze projection was recorded as the virtual gaze location. This allowed us to store gaze coordinates in the virtual world, as well as the objects foveated for each frame of the associative memory task.

As described in **Section 2.2**, a custom-built toolbox was used to parse eye movements into four categories of eye movements: saccades, post-saccadic oscillations, fixations, and smooth pursuits. The latter two categories are jointly referred to as foveations. For the present analyses, every single foveation event during the associative memory task was identified. Firing rate for each recorded neuron was computed 1) 200ms before foveation, 2) for the duration of foveation, and 3) 200ms after foveation. The virtual gaze position, as well as a table including 38 parameters related to every single foveation was computed for the present analyses. These include: trial ID; foveation type (fixation or smooth pursuit); foveation start and end time; virtual subject position (x, y, and rotation); subject speed and rotation; eye-on-screen position (x, y); virtual gaze position (x, y, z); and Boolean indicators indicating whether the foveation included each of the 20 virtual objects in the virtual maze.

For each foveation in the associative memory task, three metrics of firing rate specificity for foveated objects were used: 1) differential firing rate activity; 2) selectivity index; and 3) information content. These analyses were carried out separately for each object-pair/context associate combination. Due to the size of the foveal region, the maze floor was included in a high proportion of foveations; for this reason, the floor was removed from all foveations that also included another object in the virtual environment. These are each described in more detail in the following sections.

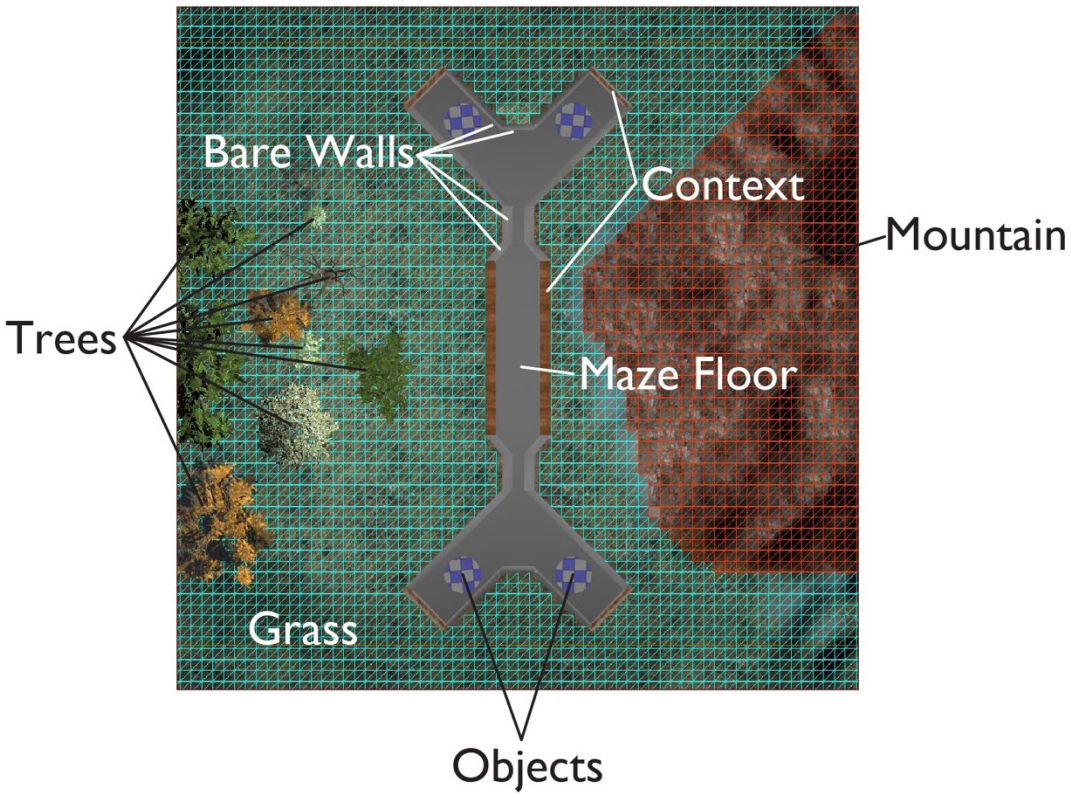


Figure 5.1. Object categories in the virtual environment

For each foveation (including smooth pursuits and fixations), all objects within three degrees of the gaze position in the maze were retrieved.

5.2.2 Learning analyses

To demonstrate that monkeys learned the importance of context in guiding behaviour in the associative memory task, a state-space was used to estimate the learning state based on previous and future trial outcomes from the perspective of an ideal observer to estimate a hidden variable (Smith et al., 2004). This produces an estimate of the learning state, as well as a 95% confidence interval of the learning state. Learning is said to have occurred when the lower 95% confidence interval of the estimated learning state exceeds 50% (Smith et al., 2004; Wirth et al., 2003).

5.2.3 Object firing rate selectivity

Each neuron's mean firing rate was computed during foveations to each object in the virtual X-Maze for each object-pair/context combination. Firing rates were deemed statistically elevated if the empirical mean for foveations on object *i* exceeded the 99.9th percentile of values when the firing rate vector was shuffled with respect to the table of foveation parameters within that object-pair/context combination.

To test the hypothesis that the proportion of neurons with statistically significant firing rates was uniformly distributed across objects, a parametric $\chi 2$ test could not be done, since the number of neurons tested for each object was not uniform. A permutation procedure was used as follows: 1) for each neuron, a Boolean vector was created, signifying the number of objects tested and the identity of objects with significant firing rates; 2) for each unit, the Boolean vector was randomly permuted, so that the number of significant objects was preserved, but the identity was not; 3) this shuffling procedure was repeated a total for a total of 999 shuffles to create a null distribution of Boolean values for each object; 4) the rank of the empirical proportions for each object were compared to the null distribution; 5) if any objects exceeded the 95th percentile of the null distribution values, the hypothesis that there was a uniform proportion of neurons with statistically significant firing rates across objects was rejected.

To compare proportions of neurons with selective firing rates for each object across learned and unlearned associations, McNemar's test of equal proportions was used.

5.2.4 Object selectivity index

A selectivity index was computed for each foveated object in the virtual environment. Selectivity index for foveated objects was computed as

$$SI = \frac{\overline{FR}_{foveations\ on\ object} - \overline{FR}_{foveations\ not\ on\ object}}{\overline{FR}_{foveations\ on\ object} + \overline{FR}_{foveations\ not\ on\ object}}$$

Selectivity index was bound between -1 and 1. Selectivity indices were deemed significant if the empirical value exceeded the 99.9th percentile of values computed when the firing rate vector was shuffled with respect to the table of foveation parameters within an object-pair/context combination.

Significance tests of proportion were completed as in **Section 5.2.2** above.

This formula was also used to compute selectivity index for foveations to each object within each single trial.

5.2.5 Gaze-object information content

The specificity of each neuron's response to different objects during foveation was quantified using information content (Ravassard et al., 2013; Skaggs et al., 1993). Information content was computed using the same formula as in Section 4.2.4, with differences in what was represented by each variable. Each neuron's information content (*I*; in bits) is defined as

$$I = \sum_{i=1}^{L} F_i \frac{\lambda_i}{\bar{\lambda}} \log_2 \frac{\lambda_i}{\bar{\lambda}}$$

where F_i is the proportion of foveations on object i, defined as

$$F_i = \frac{o_i}{\sum_{j=1}^{L} o_j}$$

and the mean firing rate per object foveation $\bar{\lambda}$ is

$$\bar{\lambda} = \sum_{i=1}^{L} F_i \lambda_i$$

Information content must always be computed with respect to a discrete random variable. One important difference between the analyses of information content presented here, and those presented in Section **3.2.3** is that the discrete variables (objects foveated) are not mutually exclusive, whereas subject positions in the maze are mutually exclusive. To mitigate effects of this bias, a null distribution of spatial information contents (and corresponding null spatial information maps) was computed for each neuron by permuting

the vector of firing rates relative to the table of foveation parameters within an object-pair/context combination prior to computing the object foveation information content. Neurons with summed foveation information content exceeding the 95th percentile of the null distribution were deemed statistically significant. In all cases, the mean of the null distribution was then subtracted from the empirical information content. The lower limit of normalized IC values was set to 0. Normalized IC values rather than raw computed IC values are reported herein.

5.2.6 Correlation between within-trial selectivity index and learning state

The relationship between learning rate object encoding and within-trial selectivity index was also examined.

For these analyses, learning state was characterized using the same computational methods as described in **Section 5.2.2**. In this case, however, learning state was simultaneously examined for trials with the highest and lowest object in both contexts. This increased the number of trials available for the current analyses, while ensuring that the object colours could be dissociated from the goal values.

Selectivity index was computed using the formula shown in **Section 5.3.4**. However, in this case, selectivity index was computed using all foveations within each trial; thus, one selectivity index was computed for each object in each trial.

The relationship between within-trial selectivity index and learning state for each trial was examined using a Spearman correlation. Empirical correlation rho values for that exceeded the 99.5th percentile of rho values with the learning states shuffled were deemed statistically significant. The proportion of neurons with a significant correlation between learning state and selectivity index for goal values, goal colours, context, and grey maze walls is reported.

5.3 Results

5.3.1 Gaze in the virtual environment

In each trial period of the associative memory task, attentional demands vary. To maximize the reward on each trial, monkeys had to consider the context and the objects presented. The context was first presented immediately upon entering the central corridor of the maze. At the end of the corridor, the maze narrowed; when the subject left the corridor,

the objects were triggered to appear in each arm of the maze; the monkey was free to choose an object with no temporal constraints. Once an object was reached and the reward was delivered, monkeys had to navigate back towards and through the corridor, to see the context for the next trial. Throughout the associative memory task, monkeys were free to move their eyes on the screen, or even to look off-screen without penalty. Thus, with unconstrained eye movements, foveations may provide a metric of overt attention while subjects were completing the task.

Monkeys spent a considerable proportion of time looking off screen during periods of the task where the objects were not yet visible in the environment (**Figure 5.2**).

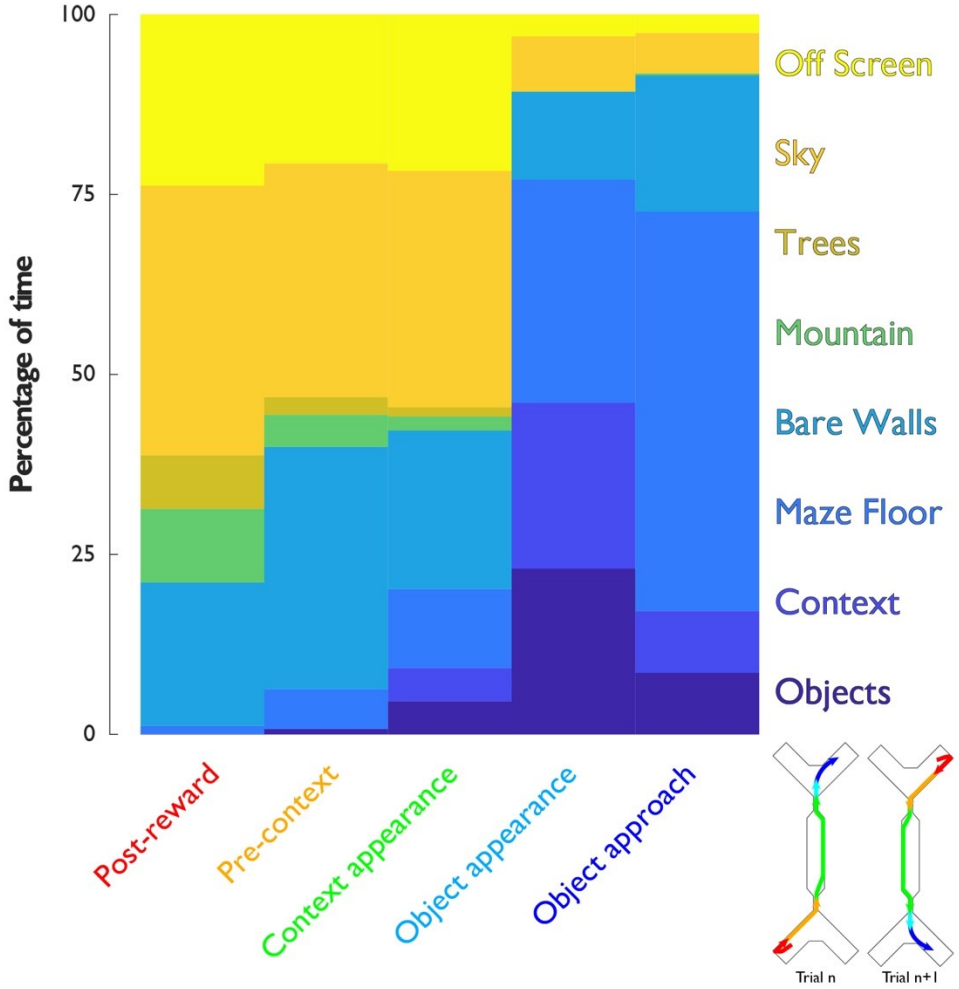


Figure 5.2. Gaze behaviour across trial periods

Gaze behaviour as a proportion of time in each trial period for a typical session in the associative memory task (session W0325). Eye movements were not constrained, and monkeys were free to gaze off-screen at any point. Monkeys spent very little time looking off screen during the Decision and Object approach periods of the task.

Across all both monkeys and all sessions, a total of 349,500 on-screen foveations were recorded during valid trials of the associative memory task (mean ± standard deviation, 9,446±2,264 foveations per session; 39±5 foveations per trial). The number of foveations varied across trial periods (Post-reward: 6.8±1.4 foveations per trial; Pre-context: 7.1±1.7 foveations per trial; Context: 13.0±1.9 foveations per trial; Decision period: 4.1±0.5 foveations per trial; Object approach: 7.9±0.8 foveations per trial).

The proportion of time foveating objects on the screen also varied considerably across trial periods. The proportion of on-screen foveations to each object category were also similar across monkeys (**Figure 5.3 B** & **C**). Monkeys spent approximately half of all foveation time on the grey maze walls in all periods of the task. The context was viewed for the largest proportion of time in the corridor of the maze. Foveations that included extra-maze elements of the environment were much less common during the Decision and Goal approach periods of the task. Finally, on-screen foveation behaviour was similar across monkeys.

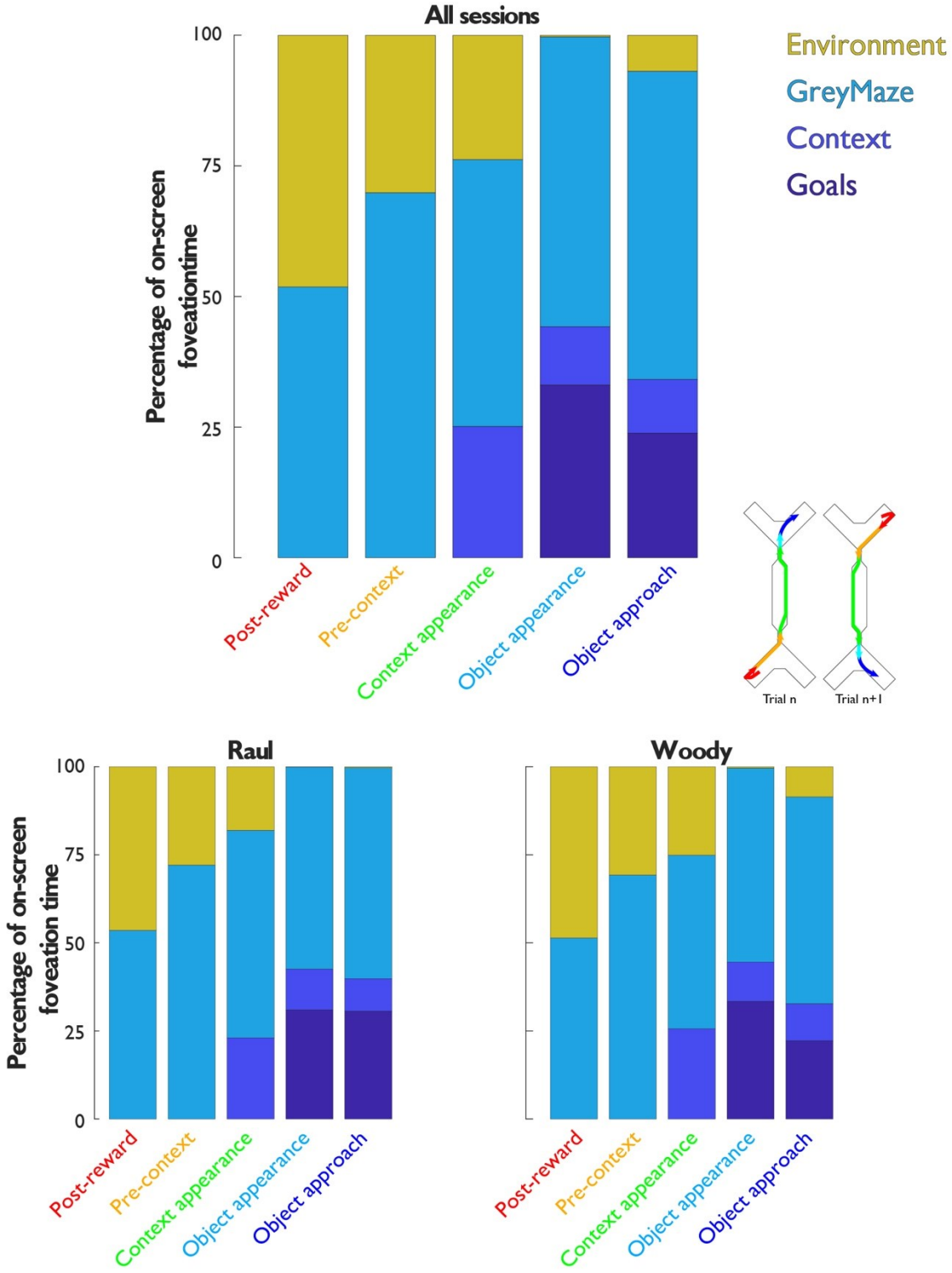


Figure 5.3. Proportion of time foveating each object type across trial periods

A) Across all sessions, foveation behaviour varied across trial periods

B & **C)** Proportion of time foveating each object category in each trial period was similar across monkeys.

5.3.2 Neuronal selectivity for foveated objects

For every foveation in the virtual environment, all objects within 3° visual angle of the centrally foveated location were known. Thus, firing rate for all foveations that included each object were computed. Thus, firing rates across all foveations on each object were computed. Spike density functions for foveations on each object can be seen in for three neurons in **Figure 5.4**. Each neuron shows a distinct firing pattern. Example neuron R0902.Hc7.2 (**Figure 5.4 A**) fires for foveations on the Wood context specifically (firing rate and selectivity index p-values <0.001). Example neuron W0304.P1M1.4 is active for foveations on the mountains (firing rate and selectivity index p-values=0.007). For neuron W0212.A0M3.2 the firing rates ranged from 11.5–14.2 Hz, and selectivity indices ranged from -0.05–0.06, and none were statistically elevated compared to their respective permutation-derived null distributions.

Across the population of neurons, a proportion are selective for all objects foveated in the X-Maze during the associative memory task (**Figure 5.5**). The proportion of selective neurons for each object was similar whether neural activity was characterized using selectivity index (open circles) or firing rate (close circles) compared to permutation-derived null distributions. To determine whether the proportion of neurons that are selective for each object is uniformly distributed, a permutation procedure was used (see **Section 5.2.3**). By shuffling the identity of objects for which each neuron was selective, it was determined that the proportion of selective neurons was not uniformly distributed across objects, with larger than expected proportions of neurons selective for foveations that included the lowest value goal, highest value goal (firing rate only), orange goal, green goal (firing rate only) and sky.

00Furthermore, information content of each neuron with respect to foveated objects was computed. Empirical information content values for 76% of neurons exceeded the 95th percentile of values derived from a permutation-derived null distribution (**Figure 5.5**, horizontal line).

The normalized information content (empirical-average null value) for all neurons is shown in **Figure 5.6**. As expected, information content values were highest for neurons deemed significant via permutation testing (two-sample Kolmogorov-Smirnov test, $p<10^{-7}$).

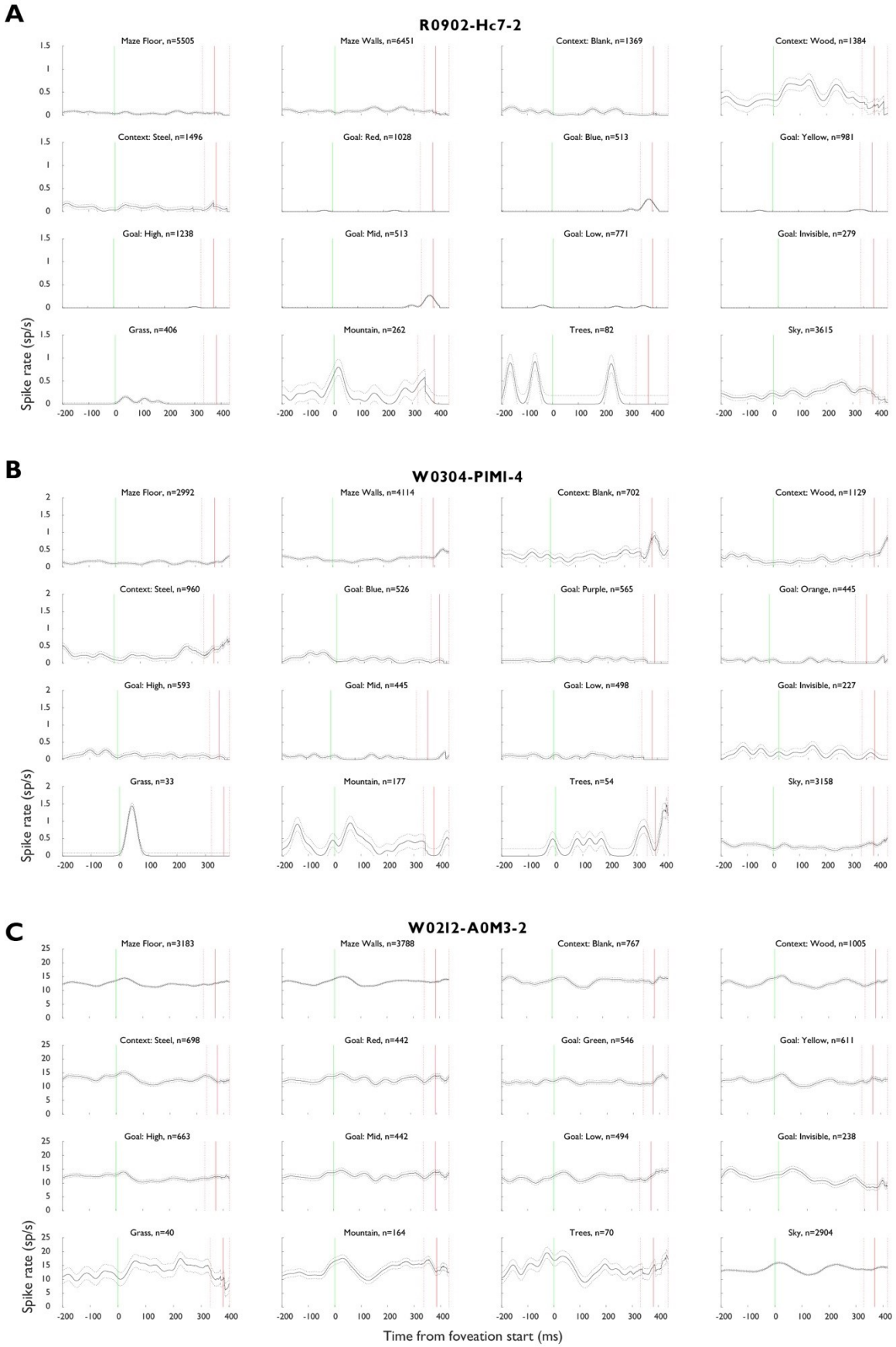

A
R0902-Hc7-2
Maze Floor, n=5505
Maze Walls, n=6451
Context: Blank, n=1369
Context: Wood, n=1384
Context: Steel, n=1496
Goal: Red, n=1028
Goal: Blue, n=513
Goal: Yellow, n=981
Goal: High, n=1238
Goal: Mid, n=513
Goal: Low, n=771
Goal: Invisible, n=279
Grass, n=406
Mountain, n=262
Trees, n=82
Sky, n=3615
Spike rate (sp/s)
B
W0304-PIMI-4
Maze Floor, n=2992
Maze Walls, n=4114
Context: Blank, n=702
Context: Wood, n=1129
Context: Steel, n=960
Goal: Blue, n=526
Goal: Purple, n=565
Goal: Orange, n=445
Goal: High, n=593
Goal: Mid, n=445
Goal: Low, n=498
Goal: Invisible, n=227
Grass, n=33
Mountain, n=177
Trees, n=54
Sky, n=3158
Spike rate (sp/s)
C
W02I2-A0M3-2
Maze Floor, n=3183
Maze Walls, n=3788
Context: Blank, n=767
Context: Wood, n=1005
Context: Steel, n=698
Goal: Red, n=442
Goal: Green, n=546
Goal: Yellow, n=611
Goal: High, n=663
Goal: Mid, n=442
Goal: Low, n=494
Goal: Invisible, n=238
Grass, n=40
Mountain, n=164
Trees, n=70
Sky, n=2904
Spike rate (sp/s)
Time from foveation start (ms)

Figure 5.4. Example spike density functions for foveations to each object

(previous page)

In all plots, the green line marks the foveation start time. The solid red line shows the median foveation end time, while dotted red lines mark quartiles.

A) Example neuron that is selective for foveations to the Wood context material

B) Example neuron that is selective for foveations on the Mountains

C) Example neuron that is not selective based on firing rate or selectivity index comparison to permutation-derived null distributions

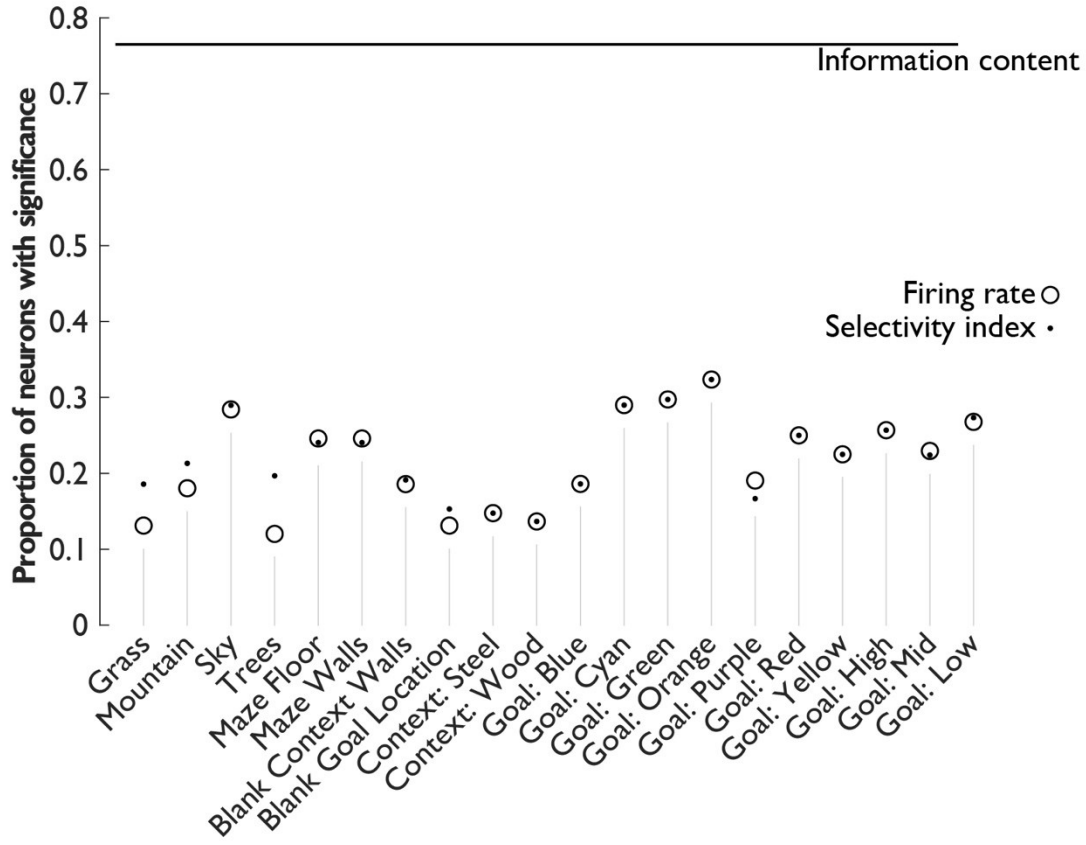


Figure 5.5. Proportion of neurons selective for each object in the X-Maze

The proportion of neurons with significant information content (horizontal line) for foveated objects, and the proportion of neurons with a significantly elevated firing rate (open circle) or selectivity index (dot) for each object. Statistical significance for each neuron was reported if the empirical value exceeded the 95th percentile (information content) or 99.9th percentile (firing rate and selectivity index) of values when object firing rates were shuffled with respect to object labels.

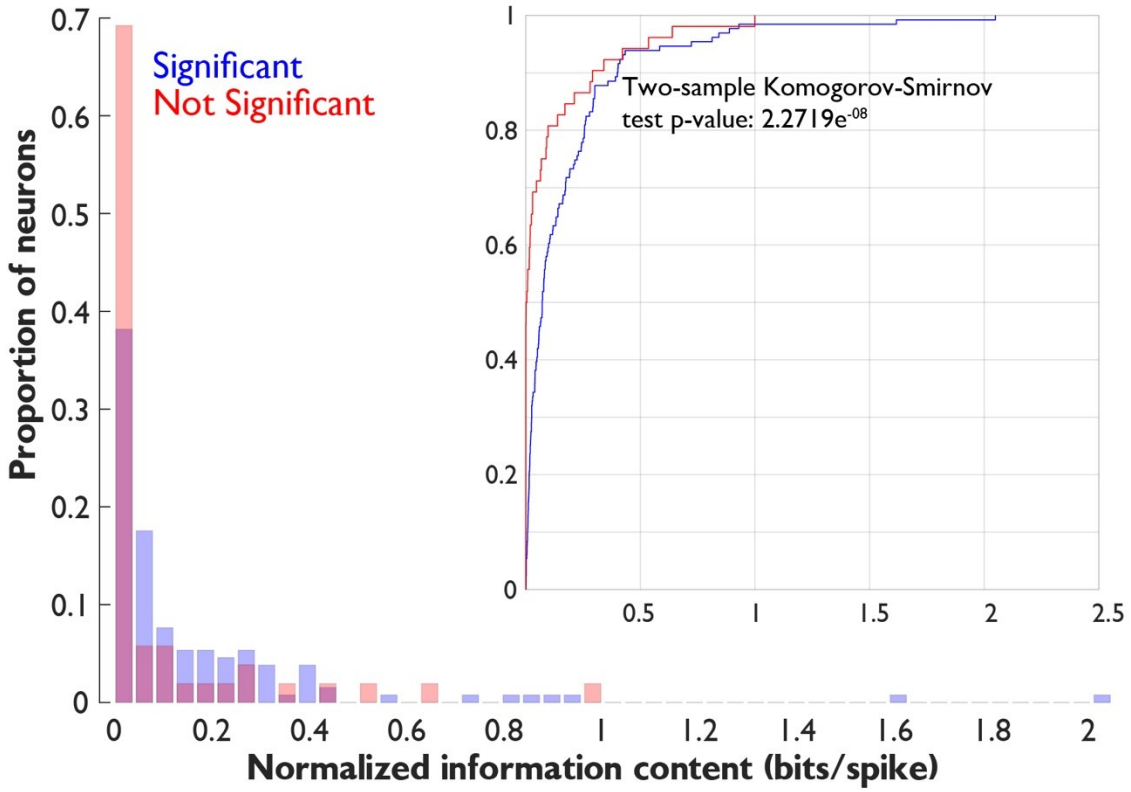


Figure 5.6. Information content for foveated objects

Distribution of normalized information content values (empirical-permutation derived null distribution mean) for all neurons that were deemed significant (blue) or not significant (red).

The distribution of information content values across these groups were significantly different, as shown in the inset.

5.3.3 Learning state across object-pair/context associations

All previous results were computed using foveations from all valid trials of the associative memory task. However, performance was not saturated for all object-pair/context associations. Therefore, learning state was quantified for each of the 6 associations encountered in a single recording session independently.

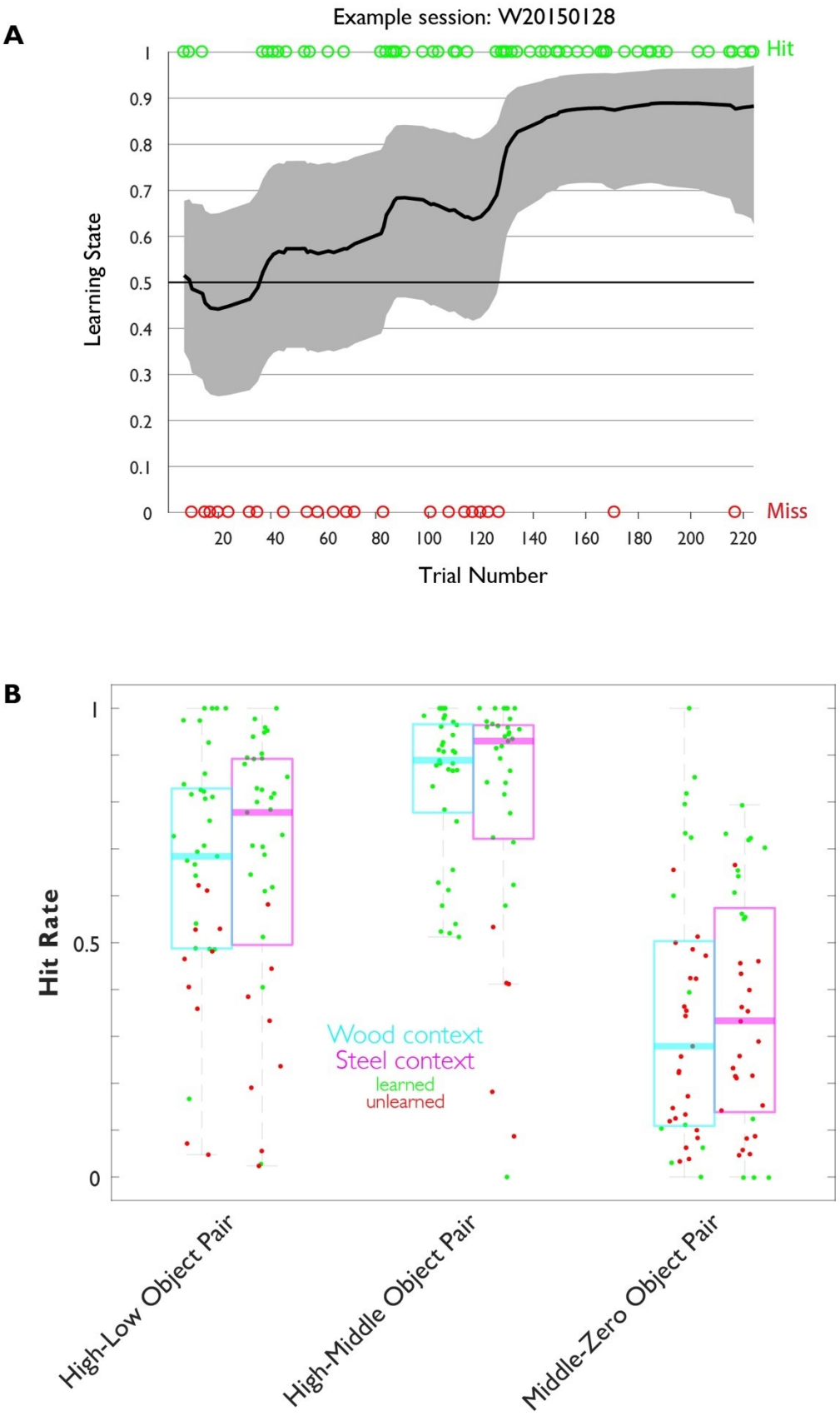
For each association, learning state and a 95% confidence interval for the learning state on each trial was quantified using a state-space model takes all trial outcomes from that association into account (Smith et al., 2004). An example of the learning curve computed using this method for trials with the highest and lowest objects present in a single session can be seen in **Figure 5.7 A**. Across all sessions, the lower 95% confidence interval exceeded chance performance in 69% of associations, with a median of 4 associations learned per session. The hit rate for learned and unlearned associations is shown in **Figure 5.7 B**. The association between the highest and lowest value object with the Wood and Steel context was learned in 78.4% and 73.0% of sessions, respectively. The association between the highest and middle reward value objects with the Wood and Steel context was learned in 100% and 86.5% of sessions, respectively. The association between the middle and lowest value object with the Wood and Steel context was learned in 40.5% and 35.1% of sessions, respectively.

Figure 5.7. Learning state estimation

(next page)

A) Trial-by trial estimation of learning state (black line) and 95% confidence interval of the learning state (shaded area). Hits and misses for each trial are denoted by green and red circles, respectively

B) Hit rate for learned and unlearned (green and red dots) for all associations in every session of the associative memory task


A
Example session: W20150128
Hit
Miss
Learning State
Trial Number
B
Hit Rate
Wood context
Steel context
learned
unlearned
High-Low Object Pair
High-Middle Object Pair
Middle-Zero Object Pair

5.3.4 Neuronal selectivity for foveated objects in learned and unlearned associations

Since learning outcomes varied across associations within a session, it is useful to examine selectivity for foveations to each object in the environment within each association separately.

Across the population of neurons, a proportion are selective for all objects foveated in the X-Maze during the associative memory task (**Figure 5.5**). The proportion of selective neurons for each object was similar whether neural activity was characterized using selectivity index (open circles) or firing rate (close circles) compared to permutation-derived null distributions. Though a greater proportion of neurons appear to be selective for specific objects during the learned associations, population distributions of normalized information content per spike did not differ between learned and unlearned associations (**Figure 5.9**; two-sample Kolmogorov-Smirnov test, p=0.09).

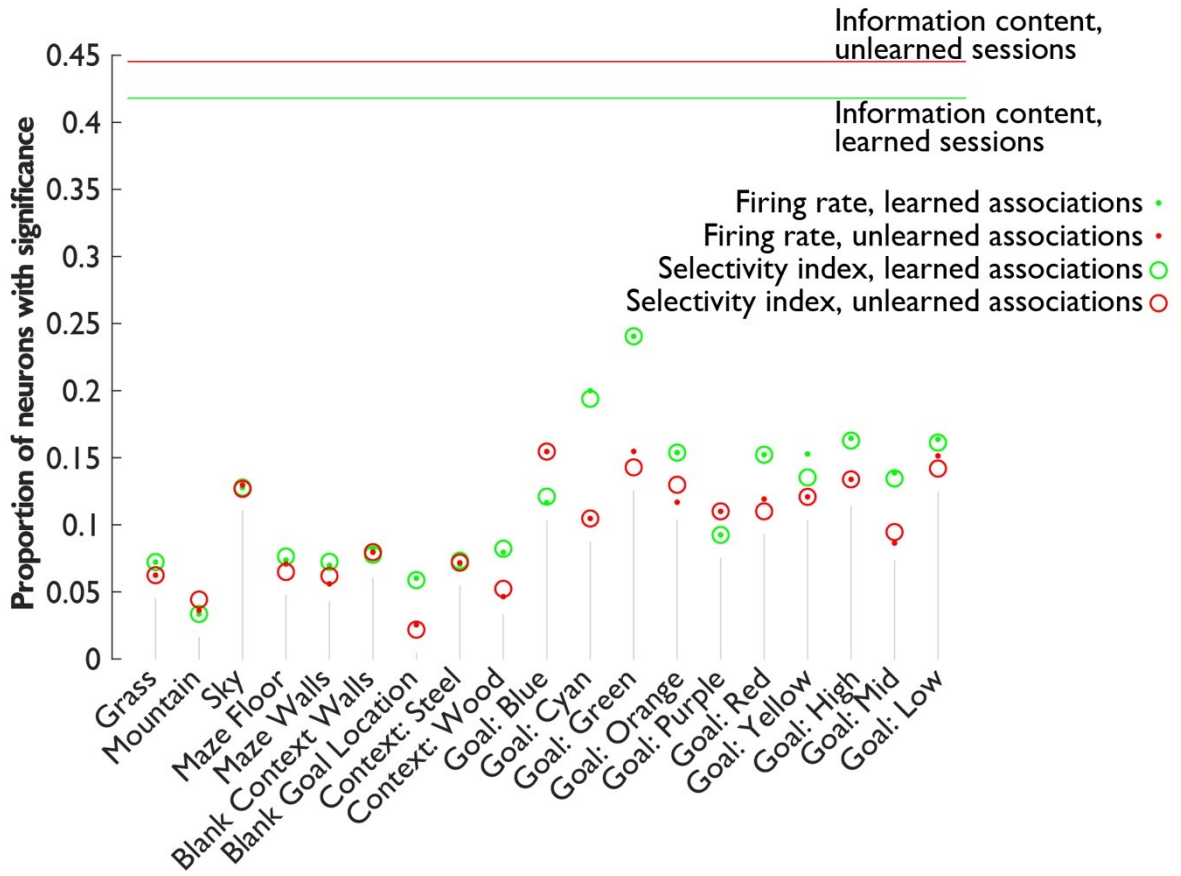


Figure 5.8. Neuronal selectivity for foveations on each object in learned and unlearned associations

Conventions are the same as in **Figure 5.5**. Green, learned associations; red, unlearned associations.

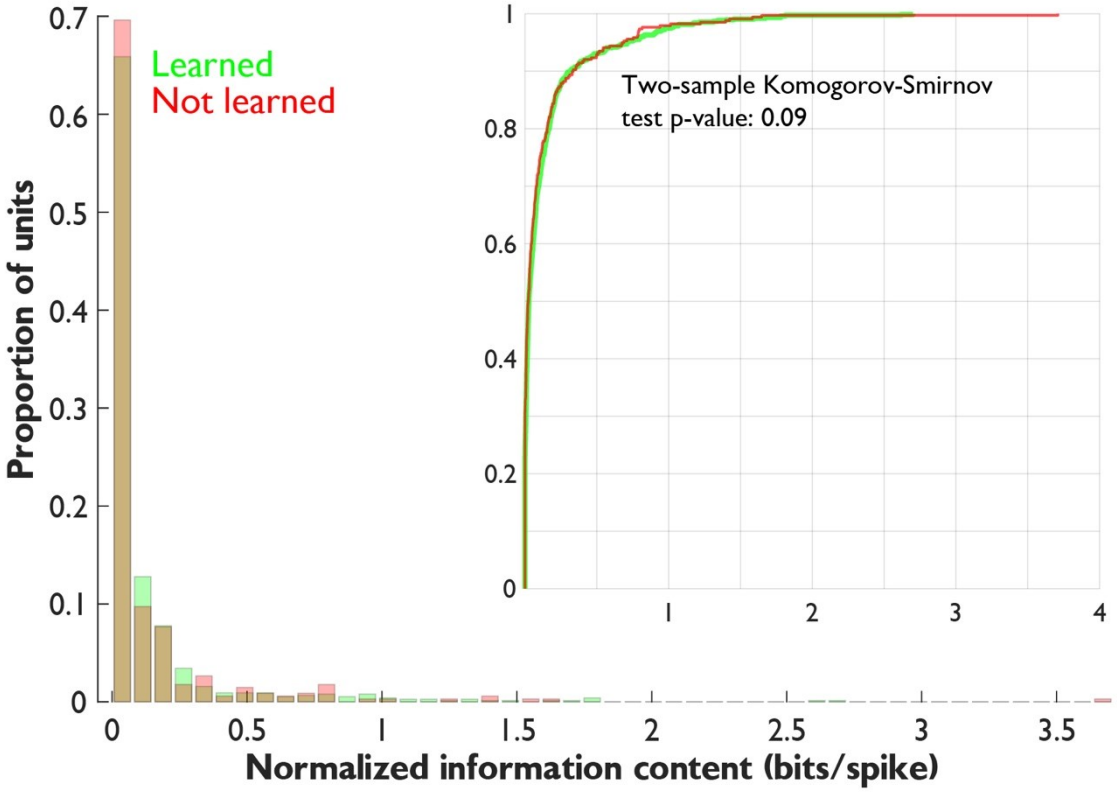


Figure 5.9. Population distributions of information content computed for learned and unlearned associations

Distribution of normalized information content values (empirical-permutation derived null distribution mean) for all neurons during learned (green) or and unlearned (red) associations.

The distribution of information content values across these groups was not significantly different, as shown in the inset.

5.3.5 Changes in neuronal selectivity as a function of learning

Across learned and unlearned sessions, the information content for foveated objects was similar. However, it is important to consider that within each association, the learning state inferred from trial outcomes was not stationary (see **Figure 5.7 A**). Therefore, for each neuron, the relationship between selectivity for each object and learning state was characterized.

The learning curve computed for all trials with the highest and lowest value objects in both contexts can be seen in **Figure 5.10**. In this session, learning is said to have been demonstrated at trial 45, when the lower bound of the 95% confidence interval exceeded chance performance. For foveations to each object in each trial, the mean firing rate and selectivity index of an example neuron from this session can also be seen **(Figure 5.10 B** & **C**, respectively). In the initial 25 trials of the session, firing rate was homogenous for foveations to the different objects in the environment. However, after this point, firing rate and within-trial selectivity index markedly increase for foveations that include the goals. Firing rate increases for foveations that include the maze floor can be attributed to the 3° visual angle foveation area used for gaze reconstruction, outlined in **Section 5.2.1**. A significant positive correlation was observed between learning state and selectivity index for foveations to the maximum value goal (Spearman correlation, $p=0.001$ compared to permutated control values).

At a population level **(Figure 5.11 B**), the largest proportion of neurons had a significant correlation between selectivity index for goal value and learning state (8.8%). The lowest proportion of significant correlations with learning state was observed for context foveations (3.6%). These results corroborate the relative proportions of neurons shown to be selective for the highest and lowest goal values compared to each context **Figure 5.5** and **Figure 5.8**.

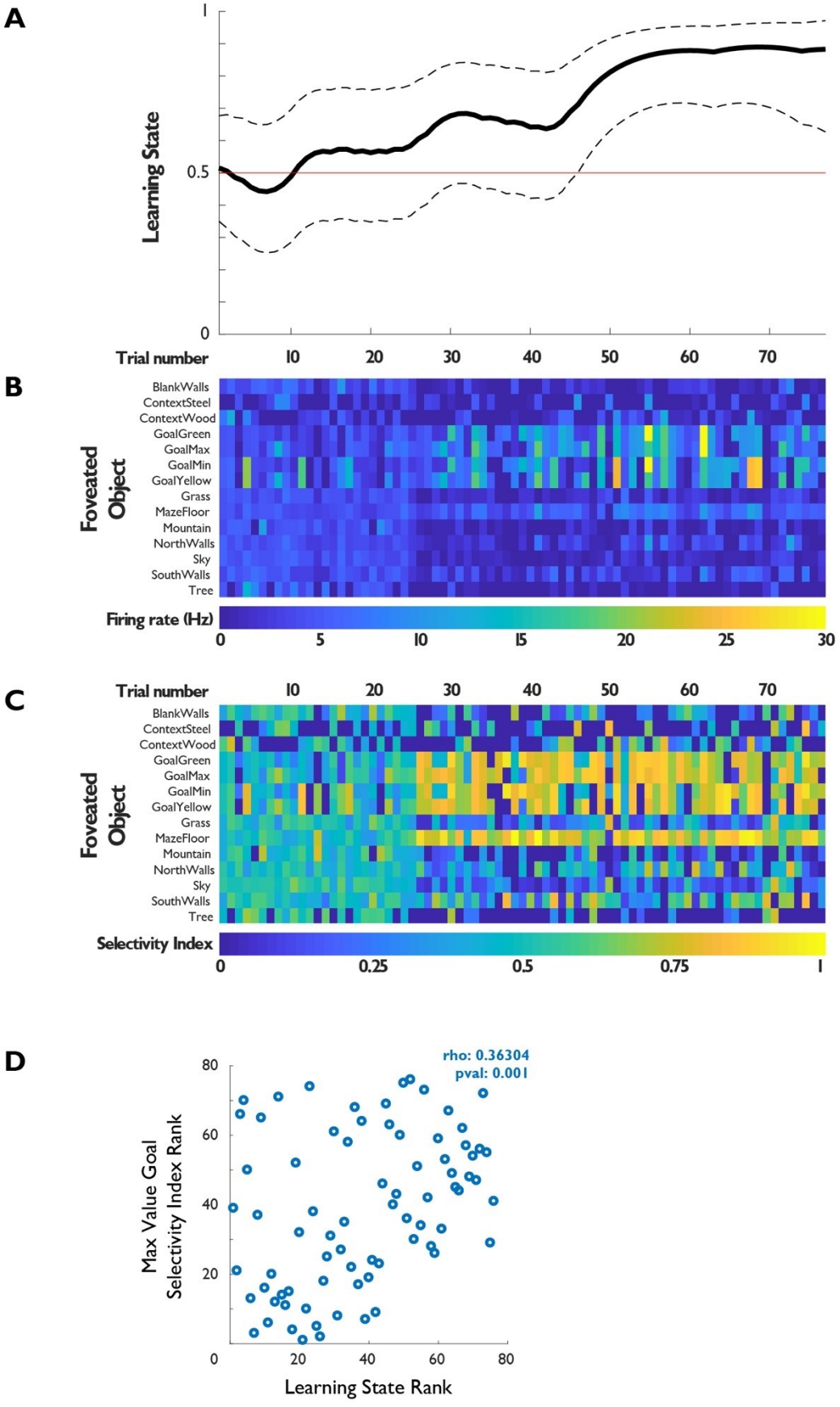

A
Learning State
1
0.5
0
Trial number
10
20
30
40
50
60
70
B
Foveated Object
BlankWalls
ContextSteel
ContextWood
GoalGreen
GoalMax
GoalMin
GoalYellow
Grass
MazeFloor
Mountain
NorthWalls
Sky
SouthWalls
Tree
Firing rate (Hz)
0
5
10
15
20
25
30
C
Trial number
Foveated Object
Selectivity Index
0
0.25
0.5
0.75
1
D
rho: 0.36304
pval: 0.001
Max Value Goal Selectivity Index Rank
Learning State Rank
0
20
40
60
80

Figure 5.10. Example neuron changes in firing rate and selectivity as a function of learning

(previous page)

A) Learning curve computed over all trials with the highest and lowest value objects present in both contexts for a single example session.

B) Rows: Each object visible in the virtual environment; columns: each column corresponds to one trial, aligned to the x-axis in A); colour scale: mean firing rate during foveations to each object within each trial

(C) Conventions are the same as in B); colour scale depicts selectivity index, which is bound between -1 and 1

D) Scatterplot showing the relationship between rank of learning state and selectivity index for foveations to the maximum value goal; each open circle corresponds to a single trial. Therefore, the number of points is equal to the length of the x-axis in plots A)-C)

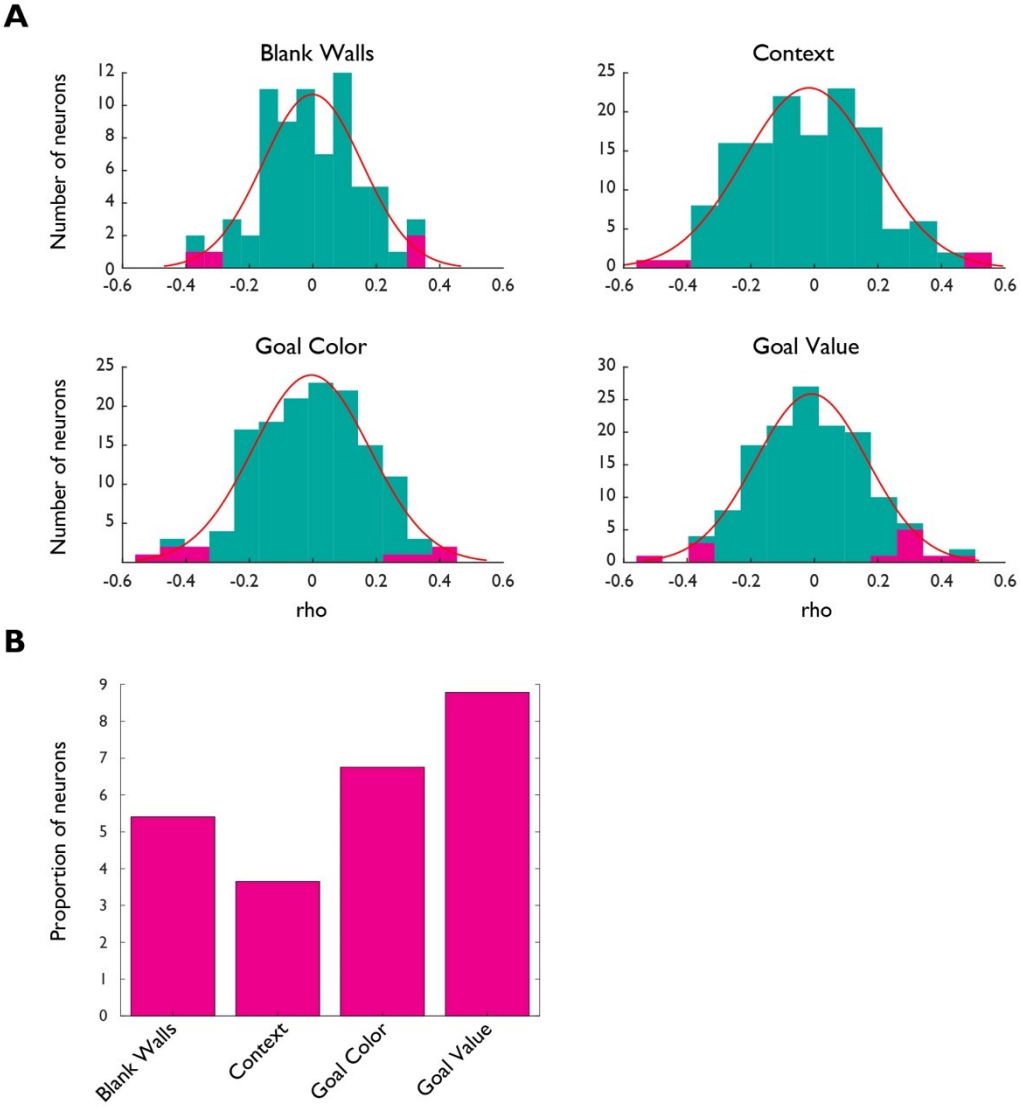


Figure 5.11. Population correlation between object selectivity and learning state

A) Distribution of rho values derived from the Spearman correlation between learning state and selectivity index for each object across all neurons

B) Proportion of neurons that show a significant correlation between learning state and object selectivity index for the different types of objects in the virtual environment

6 DISCUSSION

"Unless [one] can put the particular phenomena he himself sees under more general laws, or unless he tries to do this, he can scarcely be said to know or to be studying a thing in a very valuable sense."

Hughlings Jackson, Writings, 1931

6.1 Synopsis of Aims and Experimental Findings

In the introduction of this thesis, I described research spanning back to the early 19th century implicating the hippocampus in memory formation. This was originally due to observations of diverse hippocampal connectivity, and well-documented effects of lesions in monkeys and clinical observations in patients with hippocampal damage. Controlled lesion studies after HM showed that the hippocampus is specifically implicated in certain forms of memory. Finally, neurophysiological studies showing that changes in hippocampal firing rates correlate with behavioural measures of learning in a variety of tightly controlled tasks. However, these tasks involve highly constrained behaviour, and a very small proportion of neurons show these types of changes. In parallel to these studies of hippocampal involvement in memory, the theory that the hippocampus subserves spatial navigation flourished after the discovery of place cells in rodents. Theoretical attempts to reconcile these functions have led some groups to suggest a primacy for spatial coding in the hippocampus (Buzsáki and Moser, 2013; Knierim, 2015; Nadel, 1991; O'Keefe, 1978), while others suggest that the fundamental role of the hippocampus is memory, with physical space as just one parameter that must be conjunctively encoded in episodic memory (Eichenbaum, 2017a; Eichenbaum and N. J. Cohen, 2014). Direct comparisons of spatial and non-spatial (sensory and mnemonic) representations in hippocampal neurons are challenging due to methodological gaps between model species (Buzsáki and Moser, 2013; Eichenbaum and N. J. Cohen, 2014; Ekstrom and Ranganath, 2017; Schiller et al., 2015). Furthermore, extrapolating hippocampal coding schemes across species is complicated by diverse structural organization of sensory systems and corresponding reorganization of sensory inputs to the hippocampus (Murray et al., 2017; Preuss, 2000).

The broad goal of this thesis was to simultaneously test predictions derived from spatial and mnemonic theories of hippocampal function. **Chapter 2: General Methodology** describes a novel methodology developed for this thesis that was used to create two cognitive tasks in the same virtual environment while recording from single neurons in the monkey hippocampus. In **Chapter 3: Spatial Information in the Hippocampus**, spatial encoding in hippocampal neurons was characterized and compared across both tasks: a foraging task and an associative memory task. The observed hippocampal code for space did not generalize across tasks; the population code was most similar in the maze corridor, where behavioural demands were similar across tasks. However, the population code was distinct in the arms and branching point of the maze where the task-relevant decision was made. **Chapter 4:**

Non-spatial Information in the Hippocampus elaborates upon this finding by showing that hippocampal neurons dynamically encode trial-varying features of the associative memory task as subjects traverse the maze. **Chapter 5: Representation of Foveated Objects and Changes with Learning** the encoding of objects in the virtual environment while they were foveated. This chapter shows that encoding for all objects is evident in hippocampal neurons, not only those that are relevant to the associative memory task. However, the correlation between neuronal selectivity for object value and metrics of learning are most prevalent amongst the recorded neurons.

6.2 Pure spatial coding in the hippocampus

The hippocampus has been referred to as the GPS of the brain. This claim is supported by decades of study showing allocentric spatial firing fields of hippocampal place cells in rodents, which code for a “special” and “ineliminable” aspect of every episodic memory (Nadel, 1991). Place cells are supported by a vast network of neurons in the hippocampus and neighbouring brain areas with complementary spatial coding schemes (Hartley et al., 2014; Moser et al., 2017).

Decades after the discovery of place cells in rodents, it was believed that analogous place cells did not exist in the primate hippocampus (Eichenbaum et al., 1999). Spatially-specific responses of hippocampal neurons in spatial DR tasks were unlike allocentric rodent place cells, and their activity was confounded by other cognitive, motor and behavioural factors related to stimuli, responses, and eye movements (Cahusac et al., 1989; Colombo et al., 1998; Feigenbaum and Rolls, 1991; Rolls et al., 1989; Tamura et al., 1990; Watanabe and Niki, 1985; F. A. Wilson et al., 1990; Xiang and M. W. Brown, 1999). Several studies showed spatial firing fields for neurons recorded from the hippocampi of monkeys performing an operant joystick task that resulted in the movement of a motorized cab around a lab (Hori et al., 2003; Matsumura et al., 1999; Nishijo et al., 1997; Ono et al., 1993b). However, place fields in these tasks were defined using a liberal statistical threshold, and the confounding effects of view and other task-related factors were not quantified or controlled. Similar issues complicate the first studies of hippocampal activity in virtually navigating primates (Hori et al., 2005). The first experiments recording subject position and gaze position in the environment described spatial view cells in the hippocampus (Georges-François et al., 1999; Rolls et al., 1997), and subfield-specific effects of objects within spatial view fields (Robertson et al., 1998).

In a study with epileptic patients completing a delivery task in a virtual town, firing rates of single neurons were tested using an ANOVA for main effects of position within the environment, objects viewed in the environment, navigational goal, and interactions. Out of 55 hippocampal neurons, 24% were "bona fide place cells" with a significant main effect for place in the environment, but not view or goal. All recorded place fields were deemed direction-independent because the population average firing rate across all hippocampal place fields was not biased towards one cardinal direction (Ekstrom et al., 2003). These methods are not comparable to the methods used by Rolls and colleagues to show that monkey hippocampal neurons have spatial view fields, but not allocentric place fields. In a second study using a similar task, 18.3% of temporal lobe neurons (hippocampus, amygdala, entorhinal cortex, parahippocampal gyrus and anterior temporal cortex) showed direction-dependent place selectivity, while 7.3% were place selective irrespective of direction (Miller et al., 2013). A recent study with monkeys performing a virtual wayfinding task provides a more comprehensive analysis of hippocampal encoding (Wirth et al., 2017). In this study, 41% of hippocampal neurons had significant SIC, though only 4.8% of neurons exclusively had information content related to spatial position. Thus, spatial activity in hippocampal neurons may be largely contingent on other factors related to the subject's perceptions, actions, recent history, and recent past.

There are conspicuous differences between the spatial firing characteristics presented in this thesis, and previous descriptions of spatial response fields across species. First, the population of neurons more reliably encoded spatial position in an egocentric rather than allocentric spatial reference frame. Second, the median information content was lower than in some prominent rodent reports from the rodent literature. Thirdly, spatial firing in the studies presented may be attributed to encoding of trial-varying task features. These differences could have myriad influencing factors.

It has been proposed that major differences in visual sensory processing across rodents and primates may explain the observation of allocentric place fields in the hippocampi of rodents, and spatial response fields that depend strongly on direction and foveation location in the hippocampi of primates. In primates, the fovea provides a high-resolution field of view covering approximately 5-10° of visual angle. The fovea comprises approximately 1% of the primate visual field, but accounts for approximately 50% of the retinal output and approximately 50% of the input to primary visual cortex (Wässle et al., 1989). Thus, when primates visually explore the environment, relatively small portions of the

environment are viewed in a serial manner via eye movements. Furthermore, the same position in space can be viewed from many different locations. Rodents, on the other hand, lack a fovea, and thus do not move their eyes to bring specific portions of the environment into fine focus. Rodents can move their eyes independently to ensure a full binocular field of view above the animal at the expense of image fusion (Wallace et al., 2013). It has been estimated that the panoramic field of view provided by the rodent visual system is between 240° (Hughes, 1979) and 270° (de Araujo et al., 2001). Thus, when rodents are in a particular position of the environment, the set of possible spatial views from that location more homogenous than would be found in rotating and foveating primates. To visually sample different locations in the environment, rodents move about their environment. Thus, it has been proposed that across species, spatial view may more reliably characterize spatial response fields (de Araujo et al., 2001); in primates, this is highly confounded with gaze position in space, whereas in rodents, this is most correlated to the animal's position in space.

In addition to differences in organization and evolution of the visual system across species, it is important to consider differences in task design presented in this thesis compared to the behaviours under which the first place cells were identified in rodents. In foraging rodents, hippocampal place fields indeed appear to be allocentric; that is, whether a place cell will fire when the animal passes through a place field is not dependent on the direction of travel through the place field. When rodents are trained to traverse a linear track, however, place fields recorded in real or virtual environments are highly direction-dependent (Ravassard et al., 2013). When visual cues are tightly controlled in real and virtual environments, rodent place cells do exhibit directional preference that can be directly attributed to the visual cues (Acharya et al., 2016).

This thesis builds upon these findings by examining single neuron and population codes for a single virtual environment across cognitive tasks. The foraging task is analogous to the wayfinding task used in aforementioned recordings of hippocampal activity in real and virtually navigating primates. The associative memory task is leveraged to examine the differences in spatial coding in the same environment when the motor behaviour, landmarks, and structure of the environment were preserved, but subjects were actively engaged in a different cognitive task. The results shown in **Chapter 3: Spatial Information in the Hippocampus** initially corroborate the view that the hippocampus is critically involved in spatial mapping; individual neurons had spatial response fields and significant information content, and the population could be used to decode position. However, the hippocampal

population code for position in the virtual environment did not generalize across cognitive tasks. With the methods and population of neurons employed here, a stable representation of space was not observed even though the structure of the environment and motor behaviour necessary to navigate the environment were unchanged across tasks. Collectively, the results presented here and those from preceding literature suggest that any spatial coding observed in the primate hippocampus may be unlike allocentric place cells typically referred to in rodents across a variety of behaviours (Epstein et al., 2017; Hartley et al., 2014; Moser et al., 2017).

6.3 Non-spatial and mnemonic coding in the hippocampus

Previous examples of non-spatial stimulus encoding in hippocampal neurons have been reported across species. Subsets of hippocampal neurons and populations have been shown to "map" continuous scalar quantities other than physical space in rodents, including time (Kraus et al., 2013) and sound (Aronov et al., 2017). Stimulus selectivity in individual primate hippocampal neurons has previously been observed in discrimination (Fuster and Uyeda, 1971) and delay match to sample tasks (Cahusac et al., 1989; Colombo et al., 1998; Tamura et al., 1991). The recent study by Wirth and colleagues (Wirth et al., 2017) reported neurons that convey information related to heading direction, gaze coordinates, and "state space" (combination of these variables, and/or recent route and actions) during wayfinding. Neurons in the monkey hippocampus can be selective for faces and voices (Sliwa et al., 2016). Similarly, neurons in the hippocampus of epileptic patients can be selective for images of faces and/or facial expressions (Fried et al., 1997), and selectivity for faces and places become more alike when patients are cued to remember their association (Ison et al., 2015). It is clear from our results and others' that a wide variety of response profiles that are not directly related to physical space have been observed in hippocampal neurons across species. An ensemble of neurons with selectivities that are spatial, non-spatial and mixed could theoretically provide a holistic representation of an experience that forms the basis of an episodic memory.

Modulatory influences on single neuron and population coding for space (such as those presented in this thesis) may be interpreted as place cell remapping, as seen in studies of rodent hippocampal activity in real (Muller and Kubie, 1987) or virtual environments (Acharya et al., 2016). Several types of remapping have been defined: global, partial, local, and rate (Knierim and McNaughton, 2001; Moser et al., 2017). Global remapping occurs when all neurons with place-specific firing rearrange their preferred firing location. Partial

remapping occurs when some, but not all recorded place cells change their preferred firing location in response to a global change in the environment. Local remapping occurs when some, but not all recorded neurons change their preferred firing location in response to a localized change in the environment (e.g. addition, removal, or movement of an object or barrier). In contrast, rate remapping occurs when a neuron's preferred firing location is preserved, albeit at a significantly different rate (Leutgeb et al., 2005). The specific environmental or cognitive factors, and related thresholds that lead to each type of remapping are unclear (Moser et al., 2017).

Neither global nor rate remapping sufficiently captures the nature of cross-task changes in spatial and non-spatial encoding observed here. Similarity in cross-task models for space in the central corridor of the maze (illustrated in the cross-task confusion matrix in **Figure 3.7** and cross-task decoding model comparison in **Figure 3.9)** suggests that not all neurons with place-specific activity change their contribution to spatial decoding across tasks. Since firing rates were scaled within tasks for these analyses, rate remapping could not explain reduced prediction accuracy in cross-task spatial decoding analyses. The localized change in cross-task models of space in the arms and branches of the maze are most akin to local remapping. Beyond this, analyses throughout **Chapter 4: Non-spatial Information in the Hippocampus** and **Chapter 5: Representation of Foveated Objects and Changes with** Learning suggest that elevated firing of single neurons is attributed to sensory and mnemonic selectivity for specific features of objects at these locations in the associative memory task. The high proportion of neurons with sensory and mnemonic selectivity for non-spatial trial-varying features of the associative memory task suggest that it is the encoding of these features – rather than remapped selectivity for space per se – that explains changes in spatial representation across tasks. The nuances in spatial and non-spatial mnemonic encoding have not been previously observed in the primate hippocampus.

6.4 Theoretical Implications

These results show that the primate hippocampus encodes all experiential parameters of an experience, and these are present in the hippocampus as both perceptual and mnemonic representations. This adds to a wealth of literature suggesting that the hippocampus encodes a multitude of internal and external parameters associated with past, current and future behaviour. From this all-encompassing profile of activity, it is difficult to extract one clear psychological function to attribute to the hippocampus. This hippocampus is a polyglot

(McNaughton et al., 1996), a polymath, and the activity presented here appears to be polyphyletic. In the absence of one clear neuropsychological function of the hippocampus, one should consider alternative possibilities. One such possibility is the hippocampus ultimately fulfils a computational role in information processing, and the proximal effects of this computational role are seen across many neuropsychological functions.

6.4.1 A new approach: Neuropsychological versus computational theories of hippocampal function

A comprehensive review of the literature in **Chapter 1: Literature Review**, **Chapter 9: Appendices, I** and **Chapter 9: Appendices, II** shows that neuropsychological approaches to understanding hippocampal function are dominant. That is, researchers typically hypothesize that the hippocampus mediates a neuropsychological phenomenon, and subsequently 1) perturb the hippocampus to examine a monkey's proficiency in behaviours that require neuropsychological phenomenon (see **Chapter 9: Appendices, I**), or 2) record electrophysiological potentials in the hippocampus, and correlate them to the observation of the neuropsychological phenomenon (see **Chapter 9: Appendices, II**). Non-human primate lesion studies appear to be falling out of fashion following their zenith around the 1990s, and reversible hippocampal inactivation studies are technically challenging in non-human primates. Thus, a shift towards the correlational studies of non-human primate behaviour and hippocampal neuronal activity has been underway for decades. Indeed, the current thesis was forged from this latter mould, aiming to test tenets of spatial navigation and mnemonic theories of hippocampal function coupled with electrophysiology. There are active proponents using this approach to argue passionately that the ultimate cause of hippocampal evolution is to subserve a given neuropsychological function. Even after decades of investigation though, a survey of recent review articles suggests that there much discord between competing theories, and reconciliation of an ultimate hippocampal function in all, or even any one species is not established (Eichenbaum and N. J. Cohen, 2014; Ekstrom and Ranganath, 2017).

A limitation of electrophysiological studies such as those in **Chapter 9: Appendices, II** is that the only tractable outcome of these studies is further representational correlation; that is, a correlation between neural activity and some parameter(s) of the environment, behaviour, or cognition that is deemed statistically significant. One may argue — indeed the current thesis follows this argument —that the observation of representational correlations is an important step in understanding emergent representational categories that

are dominant in a brain area. However, a practical obstacle limits the usefulness of this type of approach to understanding hippocampal function. As the results of this thesis show in monkeys and a wealth of literature in rodents shows (see **Section 6.3)**, the hippocampus is a polyglot (McNaughton et al., 1996). It seems that the activity of hippocampal neurons can be mapped to any sensory or cognitive dimension that is relevant to subjects' behaviour at the time neural activity is being recorded. How can we understand the fundamental function of this brain area given that it seems to encode such a wide variety of parameters? An alternative approach has been ignored through much of the work discussed in the body of work discussed in **Chapter 1: Literature Review** and the **Appendices**: to suppose that hippocampal circuits have evolved to carry out an information processing function (or set of functions), and that information processing may serve a variety of neuropsychological phenomena.

At the core of many theories of hippocampal function is the observation that hippocampal neurons are frequently observed to encode conjunctive representations (Eichenbaum, 2017b). There are several notable computational theories that avoid neuropsychological explanations of hippocampal function that are compatible with conjunctive coding. The first of these proposes that the hippocampus is a memory system that uses the statistics of the recent history to compress a stream of highly correlated sensory experiences. The architecture of the hippocampus has long been compared to that of an auto-associative network (Marr, 1971; Tank and Hopfield, 1987), and it is known that sensory compression can be achieved using a simple network trained as a sparse auto-encoder (Gluck and Myers, 1993; Olshausen and Field, 1997). This type of network was recently used to compress simulated sensory experiences of an agent exploring a new environment (Benna and Fusi, *in preparation*). The network naturally produced the spatial response properties of typical hippocampal neurons. The implication of this work is that compressed sensory representations improve the efficiency of information storage for memory, produce representations that can be highly biased towards relevant portions of the environment, and explain the elevated variability of the neuronal responses characteristic of many hippocampal electrophysiological studies. Other computational work proposed that the hippocampus encodes cognitive maps that are analogous to reinforcement learning environments that focus on the encoding of temporal sequences and abstract information that is relevant for predicting the next state of the environment (Hardcastle et al., 2017; Mattar and Daw, 2018; Stachenfeld et al., 2017).

These proposed models have not been explicitly tested here, but the current data should be compared against their predictions and inform their continual development. Both computationally-inspired models are compatible with conjunctive coding (Eichenbaum, 2017b; Eichenbaum et al., 1999), but may generate more specific predictions. Models of the hippocampus as a reinforcement learning environment based on Markovian principles do not predict the observation of mnemonic representation of the previous trial parameters, as seen in **Chapter 4: Non-spatial Information in the Hippocampus** and **Chapter 5: Representation of Foveated Objects and Changes with** Learning. Whether a model of the hippocampus focused on sensory compression would generate sensory and mnemonic encoding of task features here is not yet known. In accordance with the findings of the current study though, all of these theories argue against the idea that the primate hippocampus encodes a pure and veridical representation of space, or merely maps features of the environment that are relevant to associative memory.

Predictions of the latest phenomenologically- and computationally-derived theories of hippocampal function need to be tested in greater depth and detail than could be achieved at the outset of this work. This is the next subject of discussion.

6.5 Recommendations for Future Research

To maximize the effectiveness of the next generation of studies on hippocampal function, a few important lessons can be derived from whatever successes and failures are to be found in the current work. As should be apparent based on the discussion thus far, future work should focus on: 1) testing explicit predictions and implicit assumptions of computationally-inspired theories of hippocampal function; 2) further parameterization of naturalistic behaviour; and 3) recording from large populations of neurons across hippocampal subfields.

6.5.1 Test predictions of computational theories across behaviours, not neuropsychological theories within behaviours

As previously discussed, a direct and complete refutation or an unequivocal confirmation of neuropsychological theories of hippocampal function are complicated due to the breadth of representations observed amongst hippocampal neurons. To accommodate the vast landscape of hippocampal representations that have been observed, Minsky, Marr, Hopfield, Rolls, Treves, McNaughton, and Eichenbaum have all supposed in some form that

mnemonic functions of the hippocampus are a product of the confluence of sparse representations and recurrent excitation, that mimics the architecture of an auto-associative network. New work builds upon this idea in a more tractable manner (Benna & Fusi, *in preparation*). In this work, it is theorized that the dentate gyrus and CA3 compress sensory representations (input primarily via entorhinal cortex) via divergence and recurrent inhibition. This process of sparsification of in the dentate gyrus, and competitive interactions with a high degree of recurrence in CA3 serves to remove statistical regularities in the inputs, thereby compressing sensory information so that only the unique aspects of an experience are consolidated in neural ensembles downstream in trisynaptic circuit (CA1). Through repeated experience (online) and replay (offline), these compressed neuronal ensembles of an episodic representation become linked as a co-active unit. One prediction of the model here is that novel aspects of an experience should be most clearly represented in the downstream network instantiated in CA1. By contrast, CA3 may instantiate the familiar aspects of an experience, or those that are more highly correlated with previous experience. There is a surprisingly rich literature wherein the biology of each of these subfields corroborates the predictions of this model (Bahar et al., 2011; J. D. Cohen et al., 2017; Larkin et al., 2014; Nitz and McNaughton, 2004) that is founded on computational principles of information compression.

6.5.2 Parameterize naturalistic behaviour and leverage its variability

In accordance with a focus on computational theories of hippocampal function, future studies should test theoretical predictions across a variety of naturalistic behaviours rather than within contrived and constrained behaviours characteristic of much of the non-human primate hippocampal lesion literature.

To develop a computationally-grounded theory of hippocampal function is to attempt to understand the information transformation that the hippocampus has evolved to perform. If one understands this, testing predictions of how perturbation of this information processing affects natural behaviour is paramount. Furthermore, the activity of ensembles that are believed to implement this information processing can be tested against a grounded theoretical framework.

Much of the discord amongst the studies included in **Chapter 9: Appendices, I** can be attributed to the wide variability in experimental design. Additionally, behaviour within each experiment was contrived but devoid of careful observation and parameterization. Thus, monkeys have been trained to complete wildly varying sorts of tasks, but the behaviour of

subjects in these studies is not typically monitored with rigor. Individual trial outcomes are seldom tracked; typically only trials to criterion and/or hit rate are reported. Therefore, many possible effects of hippocampal perturbation on dynamics of behaviour that occur within single trials are inaccessible. Virtual reality tasks are ideally suited to allow experimenters flexibility to design experiments that allow naturalistic exploration of the environment, while parametrizing all relevant aspects of behaviour. The associative memory task employed in the current thesis was inspired by the works of Pribram, Mishkin, Murray, Gaffan and others, but adapted for completion in a navigable virtual environment. It is the opinion of the author that the advantages gained by tracking all relevant parameters of behaviour (position in space, gaze position in space, foveated objects, recent trial history, etc.) will be essential to the development of a comprehensive understanding of the information processing function of the hippocampus across a wide range of behaviours.

6.5.3 Infer function from populations, not single neurons

Amongst neurons with sparse activity and conjunctive representations, statistics that are founded on assumptions of normally distributed firing rates may do a poor job of characterizing factors that account for neuronal variability. This is not a problem that is easily solved with any analytical method in the absence of a large dataset with many orthogonalized parameters of the environment and behaviour to model. Population-level analyses of encoding and decoding are much more useful investigative tools; the decoding analyses can be cross validated, and are robust to these single neuron activity issues. In any population of neurons, there are at least two fundamental components of variability: signal correlation and noise correlation. These components of variability may add additional structure at the population level that is impossible to assess at the single neuron level.

Noise correlations in some circumstances help the linear readout of a population of neurons with partially overlapping representations (Averbeck and Lee, 2006; M. R. Cohen and Kohn, 2011); however, these noise correlations are only visible in simultaneously recorded populations. In the current thesis, neurons were not recorded simultaneously, so noise correlations were inaccessible. The loss of this structure in non-simultaneously recorded units may have affected the population decoding accuracies reported here.

Signal correlations are critical to consider if assessing information at the population level for any neurons with conjunctive representations – alternately referred to as mixed selectivity. A population of conjunctively responsive neurons may contain more information

than single neurons even if these neurons are not recorded simultaneously (Fusi et al., 2016; Rigotti et al., 2013). Signal correlations remain intact even without simultaneity of a recorded population of units and despite trial-to-trial response variability. The information of the population of conjunctively responsive neurons does not necessarily scale linearly with the number of neurons, or the information contained in single neurons.

Conjunctive selectivity in hippocampal neurons has observed here and across many other studies at the single neuron level. For this reason, population decoding methods such as those used in the current thesis are critical to properly assess information contained by a population of these neurons. It is important to note that a vast number of rodent studies suggest that population decoding results cannot be inferred from single neuron selectivities for spatial information in the hippocampus, and provide read-out accuracy that may not be linearly related to the summed single neuron spatial specificity of the population (Meshulam et al., 2017; Stefanini et al., 2018; M. A. Wilson and McNaughton, 1993). Thus, in future studies, it is paramount that large datasets of neurons are simultaneously recorded, such that 1) cohesive estimates of information can be inferred from neurons, regardless of their sparse and conjunctive activity, and 2) the influence of signal and noise correlations can be independently assessed. This will allow for a better inference of the essential information that the hippocampus provides to its efferent brain areas.

7 EPILOGUE

The goal of this thesis was to test some fundamental tenets of prevailing theories of hippocampal function. Key findings here include that the hippocampal code for space does not generalize across tasks in virtually navigating monkeys; not even a subset of neurons encoded space in a cognitively invariant manner. Along with changes in activity across tasks, specific sensory and mnemonic representations relevant to associative memory were observed, and changes in these representations sometimes tracked changes in task learning. However, all objects in the environment were represented in a portion of hippocampal neurons. Instead of framing the hippocampus as the brain's Global Positional System, the spatial, sensory, and mnemonic encoding observed here better reflect the processes inherent in Tulving's General Abstract Processing System (Tulving, 1985). In such a system, adaptive representations could provide the basis for learning and storing information across behaviourally relevant dimensions in a context-dependent manner. Future work should seek to understand hippocampal function not only within individual tasks, but across a variety of behaviours; this approach may yield a deeper and more fundamental insight about the information processing performed across the unique anatomical structure of the hippocampus, and better explain the representations observed at the single neuron and population level.

8 REFERENCES

Acharya, L., Aghajan, Z.M., Vuong, C., Moore, J.J., Mehta, M.R., 2016. Causal Influence of Visual Cues on Hippocampal Directional Selectivity. Cell 164, 197–207. doi:10.1016/j.cell.2015.12.015

Angeli, S.J., Murray, E.A., Mishkin, M., 1993. Hippocampectomized monkeys can remember one place but not two. Neuropsychologia 31, 1021–1030.

Aradillas, E., Libon, D.J., Schwartzman, R.J., 2011. Acute loss of spatial navigational skills in a case of a right posterior hippocampus stroke. Journal of the Neurological Sciences 308, 144–146. doi:10.1016/j.jns.2011.06.026

Aronov, D., Nevers, R., Tank, D.W., 2017. Mapping of a non-spatial dimension by the hippocampal-entorhinal circuit. Nature 543, 719–722. doi:10.1038/nature21692

Asaad, W.F., Rainer, G., Miller, E.K., 1998. Neural Activity in the Primate Prefrontal Cortex during Associative Learning. Neuron 21, 1399–1407. doi:10.1016/S0896-6273(00)80658-3

Averbeck, B.B., Lee, D., 2006. Effects of noise correlations on information encoding and decoding. J. Neurophysiol. 95, 3633–3644. doi:10.1152/jn.00919.2005

Bahar, A.S., Shirvalkar, P.R., Shapiro, M.L., 2011. Memory-guided learning: CA1 and CA3 neuronal ensembles differentially encode the commonalities and differences between situations. J. Neurosci. 31, 12270–12281. doi:10.1523/JNEUROSCI.1671-11.2011

Banta Lavenex, P., Lavenex, P., 2009. Spatial memory and the monkey hippocampus: not all space is created equal. Hippocampus 19, 8–19. doi:10.1002/hipo.20485

Baxter, M.G., Murray, E.A., 2001a. Opposite relationship of hippocampal and rhinal cortex damage to delayed nonmatching-to-sample deficits in monkeys. Hippocampus 11, 61–71. doi:10.1002/1098-1063(2001)11:1<61::AID-HIPO1021>3.0.CO;2-Z

Baxter, M.G., Murray, E.A., 2001b. Effects of hippocampal lesions on delayed nonmatching-to-sample in monkeys: a reply to Zola and Squire (2001). Hippocampus 11, 201–203. doi:10.1002/hipo.1037

Bechterew, von, W., 1900. Demonstration Eines Gehirns Mit Zerstörung Der Vorderen Und Inneren Theile Der Hirnrinde Beider Schläfenlappen. Neurol. Centralbl. 19, 990–991.

Blonde, J.D., Roussy, M., Luna, R., Mahmoudian, B., Gulli, R.A., Barker, K.C., Lau, J.C., Martinez-Trujillo, J.C., 2018. Customizable cap implants for neurophysiological experimentation. J. Neurosci. Methods 304, 103–117. doi:10.1016/j.jneumeth.2018.04.016

Blum, J.S., Chow, K.L., Pribram, K.H., 1950. A behavioral analysis of the organization of the parieto-temporo-preoccipital cortex. J. Comp. Neurol. 93, 53–100.

Broca, P., 2015. Comparative anatomy of the cerebral convolutions. Journal of Comparative Neurology 523, 2501–2554. doi:10.1002/cne.23856

Brodal, A., 1947. The Hippocampus and the Sense of Smell. Brain 70, 179–222. doi:10.1093/brain/70.2.179

Brown, M.W., 1982. Effect of context on the response of single units recorded from the hlppocampal region of behaviorally trained monkeys., in: Marsan, C.A., Matthies, H. (Eds.), **Neuronal Plasticity and Memory Formation: Proceedings of the 6th International Neurobiological Symposium on Learning and Memory**. New York, pp. 557–573.

Brown, M.W., Horn, G., 1978. Context dependent neuronal responses recorded from hippocampal region of trained monkeys [proceedings]. J. Physiol. (Lond.) 282, 15P–16P.

Brown, S., Schäfer, E.A., 1888. XI. An investigation into the functions of the occipital and temporal lobes of the monkey's brain. Phil. Trans. R. Soc. Lond. B 179, 303–327. doi:10.1098/rstb.1888.0011

Buzsáki, G., 2006. Rhythms of the Brain. Oxford University Press, New York.

Buzsáki, G., Moser, E.I., 2013. Memory, navigation and theta rhythm in the hippocampal-entorhinal system. Nat. Neurosci. 16, 130–138. doi:10.1038/nn.3304

Cahusac, P.M., Miyashita, Y., Rolls, E.T., 1989. Responses of hippocampal formation neurons in the monkey related to delayed spatial response and object-place memory tasks. Behav. Brain Res. 33, 229–240. doi:10.1016/S0166-4328(89)80118-4

Cameron, K.A., Yashar, S., Wilson, C.L., Fried, I., 2001. Human hippocampal neurons predict how well word pairs will be remembered. Neuron 30, 289–298.

Clark, I.A., Maguire, E.A., 2016. Remembering Preservation in Hippocampal Amnesia. Annual Review of Psychology 67, 51–82. doi:10.1146/annurev-psych-122414-033739

Clark, R.E., 2018. Current Topics Regarding the Function of the Medial Temporal Lobe Memory System. Curr Top Behav Neurosci 10, 455–30. doi:10.1007/7854_2017_36

Cohen, J., 1960. A coefficient of agreement for nominal scales. Educational and psychological measurement.

Cohen, J.D., Bolstad, M., Lee, A.K., 2017. Experience-dependent shaping of hippocampal CA1 intracellular activity in novel and familiar environments. eLife Sciences 6, 17687. doi:10.7554/eLife.23040

Cohen, M.R., Kohn, A., 2011. Measuring and interpreting neuronal correlations. Nat. Neurosci. 14, 811–819. doi:10.1038/nn.2842

Colombo, M., Fernandez, T., Nakamura, K., Gross, C.G., 1998. Functional Differentiation Along the Anterior-Posterior Axis of the Hippocampus in Monkeys. J. Neurophysiol. 80, 1002–1005. doi:10.1152/jn.1998.80.2.1002

Cordeau, J.P., Mahut, H., 1964. Some Long–Term Effects of Temporal Lobe Resections on Auditory and Visual Discrimination in Monkeys. Brain 87, 177–190. doi:10.1093/brain/87.1.177

Correll, R.E., Scoville, W.B., 1967. Significance of delay in the performance of monkeys with medial temporal lobe resections. Experimental Brain Research 4, 85–96.

Correll, R.E., Scoville, W.B., 1965. Effects of medial temporal lesions on visual discrimination performance. J Comp Physiol Psychol 60, 175–181.

Corrigan, B.W., Gulli, R.A., Doucet, G., Martinez-Trujillo, J.C., 2017. Characterizing eye movement behaviors and kinematics of non-human primates during virtual navigation tasks. J Vis 17, 15–15. doi:10.1167/17.12.15

de Araujo, I.E., Rolls, E.T., Stringer, S.M., 2001. A view model which accounts for the spatial fields of hippocampal primate spatial view cells and rat place cells. Hippocampus 11, 699–706. doi:10.1002/hipo.1085

Delay, J., Brion, S., 1969. Le syndrome de Korsakoff. Masson, Paris.

Dember, W.N., Fowler, H., 1958. Spontaneous alternation behavior. Psychol Bull 55, 412–428.

Dodds, W.J., 1878. Localisation of Functions of the Brain: Being an Historical and Critical Analysis of the Question. J Anat Physiol 12, 636–660.

Doucet, G., Gulli, R.A., Martinez-Trujillo, J.C., 2016. Cross-species 3D virtual reality toolbox for visual and cognitive experiments. J. Neurosci. Methods 266, 84–93. doi:10.1016/j.jneumeth.2016.03.009

Drachman, D.A., Ommaya, A.K., 1964. Memory And the Hippocampal Complex. Arch. Neurol. 10, 411–425. doi:10.1001/archneur.1964.00460160081008

Eichenbaum, H., 2017a. The role of the hippocampus in navigation is memory. J. Neurophysiol. 117, jn.00005.2017–1796. doi:10.1152/jn.00005.2017

Eichenbaum, H., 2017b. Barlow versus Hebb: When is it time to abandon the notion of feature detectors and adopt the cell assembly as the unit of cognition? Neurosci. Lett. doi:10.1016/j.neulet.2017.04.006

Eichenbaum, H., Cohen, N.J., 2014. Can We Reconcile the Declarative Memory and Spatial Navigation Views on Hippocampal Function? Neuron 83, 764–770. doi:10.1016/j.neuron.2014.07.032

Eichenbaum, H., Dudchenko, P.A., Wood, E., Shapiro, M., Tanila, H., 1999. The hippocampus, memory, and place cells: is it spatial memory or a memory space? Neuron 23, 209–226.

Ekstrom, A.D., Kahana, M.J., Caplan, J.B., Fields, T.A., Newman, E.L., Fried, I., 2003. Cellular networks underlying human spatial navigation. Nature 425, 184–188. doi:10.1038/nature01964

Ekstrom, A.D., Ranganath, C., 2017. Space, time, and episodic memory: The hippocampus is all over the cognitive map. Hippocampus 27, 9769. doi:10.1002/hipo.22750

Elward, R.L., Vargha-Khadem, F., 2018. Semantic memory in developmental amnesia. Neurosci. Lett. 680, 23–30. doi:10.1016/j.neulet.2018.04.040

Epstein, R.A., Patai, E.Z., Julian, J.B., Spiers, H.J., 2017. The cognitive map in humans: spatial navigation and beyond. Nat. Neurosci. 20, 1504–1513. doi:10.1038/nn.4656

Fan, R.-E., Chang, K.-W., Hsieh, C.-J., Wang, X.-R., Lin, C.-J., 2008. LIBLINEAR: A Library for Large Linear Classification. The Journal of Machine Learning Research 9, 1871–1874.

Feigenbaum, J.D., Rolls, E.T., 1991. Allocentric and egocentric spatial information processing in the hippocampal formation of the behaving primate 19, 21–40. doi:10.1007/BF03337953

Ferrier, D., 1886. Functions of the Brain, 2nd ed. G.P. Putnam's Sons, New York.

Fried, I., MacDonald, K.A., Wilson, C.L., 1997. Single Neuron Activity in Human Hippocampus and Amygdala during Recognition of Faces and Objects. Neuron 18, 753–765. doi:10.1016/S0896-6273(00)80315-3

Friedman, J., Hastie, T., Tibshirani, R., 2010. Regularization Paths for Generalized Linear Models via Coordinate Descent. J Stat Softw 33, 1–22. doi:10.1109/TPAMI.2005.127

Furuya, Y., Matsumoto, J., Hori, E., Boas, C.V., Tran, A.H., Shimada, Y., Ono, T., Nishijo, H., 2014. Place-related neuronal activity in the monkey parahippocampal gyrus and hippocampal formation during virtual navigation. Hippocampus 24, 113–130. doi:10.1002/hipo.22209

Fusi, S., Miller, E.K., Rigotti, M., 2016. Why neurons mix: high dimensionality for higher cognition. Current Opinion in Neurobiology 37, 66–74. doi:10.1016/j.conb.2016.01.010

Fuster, J.M., Uyeda, A.A., 1971. Reactivity of limbic neurons of the monkey to appetitive and aversive signals. Electroencephalogr Clin Neurophysiol 30, 281–293. doi:10.1016/0013-4694(71)90111-8

Gaffan, D., 1994. Scene-specific memory for objects: a model of episodic memory impairment in monkeys with fornix transection. 6, 305–320. doi:10.1162/jocn.1994.6.4.305

Gaffan, D., 1974. Recognition impaired and association intact in the memory of monkeys after transection of the fornix. J Comp Physiol Psychol 86, 1100–1109.

Gaffan, D., Harrison, S., 1984. Reversal learning by fornix-transected monkeys. Q J Exp Psychol B 36, 223–234. doi:10.1080/14640748408402204

Gaffan, D., Saunders, R.C., 1985. Running recognition of configural stimuli by fornix-transected monkeys. Q J Exp Psychol B 37, 61–71. doi:10.1080/14640748508402087

Gelbard-Sagiv, H., Mukamel, R., Harel, M., Malach, R., Fried, I., 2008. Internally generated reactivation of single neurons in human hippocampus during free recall. Science 322, 96–101. doi:10.1126/science.1164685

Georges-François, P., Rolls, E.T., Robertson, R.G., 1999. Spatial view cells in the primate hippocampus: allocentric view not head direction or eye position or place. Cereb. Cortex 9, 197–212.

Gergen, J.A., MacLean, P.D., 1964. The Limbic System: Photic activation of limbic cortical areas in the squirrel monkey. Ann. N. Y. Acad. Sci. 117, 69–87.

Glees, P., Griffith, H.B., 1952. Bilateral Destruction of the Hippocampus (Cornu Ammonis) in a Case of Dementia. Mschr Psychiat Neurol 123, 193–204. doi:10.1159/000140010

Gluck, M.A., Myers, C.E., 1993. Hippocampal mediation of stimulus representation: a computational theory. Hippocampus 3, 491–516. doi:10.1002/hipo.450030410

Green, J.D., Arduini, A.A., 1954. Hippocampal electrical activity in arousal. J. Neurophysiol. 17, 533–557. doi:10.1152/jn.1954.17.6.533

Hardcastle, K., Ganguli, S., Giocomo, L.M., 2017. Cell types for our sense of location: where we are and where we are going. Nat. Neurosci. 20, 1474–1482. doi:10.1038/nn.4654

Harlow, H.F., Bromer, J.A., 1938. A test-apparatus for monkeys. The Psychological Record 2, 434–436. doi:10.1007/bf03393227

Hartley, T., Lever, C., Burgess, N., O'Keefe, J., 2014. Space in the brain: how the hippocampal formation supports spatial cognition. Philos. Trans. R. Soc. Lond., B, Biol. Sci. 369, 20120510–20120510. doi:10.1098/rstb.2012.0510

Hori, E., Nishio, Y., Kazui, K., Umeno, K., Tabuchi, E., Sasaki, K., Endo, S., Ono, T., Nishijo, H., 2005. Place-related neural responses in the monkey hippocampal formation in a virtual space. Hippocampus 15, 991–996. doi:10.1002/hipo.20108

Hori, E., Tabuchi, E., Matsumura, N., Tamura, R., Eifuku, S., Endo, S., Nishijo, H., Ono, T., 2003. Representation of place by monkey hippocampal neurons in real and virtual translocation. Hippocampus 13, 190–196. doi:10.1002/hipo.10062

Hughes, A., 1979. A schematic eye for the rat. Vision Res. 19, 569–588. doi:10.1016/0042-6989(79)90143-3

Ison, M.J., Quian Quiroga, R., Fried, I., 2015. Rapid Encoding of New Memories by Individual Neurons in the Human Brain. Neuron 87, 220–230. doi:10.1016/j.neuron.2015.06.016

Jones, B., Mishkin, M., 1972. Limbic lesions and the problem of stimulus—Reinforcement associations. Experimental Neurology 36, 362–377. doi:10.1016/0014-4886(72)90030-1

Jutras, M.J., Buffalo, E.A., 2010. Recognition memory signals in the macaque hippocampus. Proc. Natl. Acad. Sci. U.S.A. 107, 401–406. doi:10.1073/pnas.0908378107

Killian, N.J., Jutras, M.J., Buffalo, E.A., 2012. A map of visual space in the primate entorhinal cortex. Nature 491, 761–764. doi:10.1038/nature11587

Kimble, D.P., Pribram, K.H., 1963. Hippocampectomy and behavior sequences. Science 139, 824–825.

Klüver, H., Bucy, P.C., 1939. Preliminary Analysis of Functions of the Temporal Lobes in Monkeys. Archives of Neurology and Psychiatry 42, 979. doi:10.1001/archneurpsyc.1939.02270240017001

Klüver, H., Bucy, P.C., 1938. An Analysis of Certain Effects of Bilateral Temporal Lobectomy in the Rhesus Monkey, with Special Reference to "Psychic Blindness." The Journal of Psychology 5, 33–54. doi:10.1080/00223980.1938.9917551

Klüver, H., Bucy, P.C., 1937. "Psychic Blindness" and Other Symptoms Following Bilateral Temporal Lobectomy in Rhesus Monkeys. AJP 119, 352–353.

Knierim, J.J., 2015. The hippocampus. Curr. Biol. 25, R1116–R1121. doi:10.1016/j.cub.2015.10.049

Knierim, J.J., McNaughton, B.L., 2001. Hippocampal place-cell firing during movement in three-dimensional space. J. Neurophysiol. 85, 105–116. doi:10.1152/jn.2001.85.1.105

Kraus, B.J., Robinson, R.J., White, J.A., Eichenbaum, H., Hasselmo, M.E., 2013. Hippocampal "time cells": time versus path integration. Neuron 78, 1090–1101. doi:10.1016/j.neuron.2013.04.015

Larkin, M.C., Lykken, C., Tye, L.D., Wickelgren, J.G., Frank, L.M., 2014. Hippocampal output area CA1 broadcasts a generalized novelty signal during an object-place recognition task. Hippocampus 24, 773–783. doi:10.1002/hipo.22268

Leutgeb, S., Leutgeb, J.K., Barnes, C.A., Moser, E.I., McNaughton, B.L., Moser, M.-B., 2005. Independent codes for spatial and episodic memory in hippocampal neuronal ensembles. Science 309, 619–623. doi:10.1126/science.1114037

Lewis, F.T., 1923. The significance of the term Hippocampus. Journal of Comparative Neurology 35, 213–230. doi:10.1002/cne.900350303

Ludvig, N., Tang, H.M., Gohil, B.C., Botero, J.M., 2004. Detecting location-specific neuronal firing rate increases in the hippocampus of freely-moving monkeys. Brain Res. 1014, 97–109. doi:10.1016/j.brainres.2004.03.071

Maguire, E.A., Intraub, H., Mullally, S.L., 2016. Scenes, Spaces, and Memory Traces: What Does the Hippocampus Do? Neuroscientist 22, 432–439. doi:10.1177/1073858415600389

Mahut, H., 1972. A selective spatial deficit in monkeys after transection of the fornix. Neuropsychologia 10, 65–74. doi:10.1016/0028-3932(72)90043-7

Mahut, H., 1971. Spatial and object reversal learning in monkeys with partial temporal lobe ablations. Neuropsychologia 9, 409–424. doi:10.1016/0028-3932(71)90005-4

Mahut, H., Cordeau, J.-P., 1963. Spatial reversal deficit in monkeys with amygdalohippocampal ablations. Experimental Neurology 7, 426–434. doi:10.1016/0014-4886(63)90023-2

Mahut, H., Zola, S.M., 1973. A non-modality specific impairment in spatial learning after fornix lesions in monkeys. Neuropsychologia 11, 255–269. doi:10.1016/0028-3932(73)90037-7

Majka, P., Kublik, E., Furga, G., Wójcik, D.K., 2012. Common atlas format and 3D brain atlas reconstructor: infrastructure for constructing 3D brain atlases. Neuroinformatics 10, 181–197. doi:10.1007/s12021-011-9138-6

Malkova, L., Mishkin, M., 2003. One-trial memory for object-place associations after separate lesions of hippocampus and posterior parahippocampal region in the monkey. J. Neurosci. 23, 1956–1965.

Markov, N.T., Ercsey-Ravasz, M.M., Ribeiro Gomes, A.R., Lamy, C., Magrou, L., Vezoli, J., Misery, P., Falchier, A., Quilodran, R., Gariel, M.A., Sallet, J., Gamanut, R., Huissoud, C., Clavagnier, S., Giroud, P., Sappey-Marinier, D., Barone, P., Dehay, C., Toroczkai, Z., Knoblauch, K., Van Essen, D.C., Kennedy, H., 2014. A weighted and directed interareal connectivity matrix for macaque cerebral cortex. Cereb. Cortex 24, 17–36. doi:10.1093/cercor/bhs270

Marr, D., 1971. Simple memory: a theory for archicortex. Phil. Trans. R. Soc. B 262, 23–81.

Matsumura, N., Nishijo, H., Tamura, R., Eifuku, S., Endo, S., Ono, T., 1999. Spatial- and task-dependent neuronal responses during real and virtual translocation in the monkey hippocampal formation. J. Neurosci. 19, 2381–2393.

Mattar, M.G., Daw, N.D., 2018. Prioritized memory access explains planning and hippocampal replay. bioRxiv 225664. doi:10.1101/225664

McNaughton, B.L., Barnes, C.A., Gerrard, J.L., Gothard, K.M., Jung, M.W., Knierim, J.J., Kudrimoti, H., Qin, Y., Skaggs, W.E., Suster, M., Weaver, K.L., 1996. Deciphering the

hippocampal polyglot: the hippocampus as a path integration system. J. Exp. Biol. 199, 173–185.

Meshulam, L., Gauthier, J.L., Brody, C.D., Tank, D.W., Bialek, W., 2017. Collective Behavior of Place and Non-place Neurons in the Hippocampal Network. Neuron 96, 1178–1191.e4. doi:10.1016/j.neuron.2017.10.027

Meyer, A.C., 1971. Historical aspects of cerebral anatomy. Oxford University Press.

Miller, J.F., Neufang, M., Solway, A., Brandt, A., Trippel, M., Mader, I., Hefft, S., Merkow, M., Polyn, S.M., Jacobs, J., Kahana, M.J., Schulze-Bonhage, A., 2013. Neural activity in human hippocampal formation reveals the spatial context of retrieved memories. Science 342, 1111–1114. doi:10.1126/science.1244056

Milner, B., Penfield, W., 1955. The effect of hippocampal lesions on recent memory. Trans Am Neurol Assoc 42–48.

Mishkin, M., 1978. Memory in monkeys severely impaired by combined but not by separate removal of amygdala and hippocampus. Nature 273, 297–298. doi:10.1038/273297a0

Mishkin, M., 1954. Visual Discrimination Performance Following Partial Ablations of the Temporal Lobe: II. Ventral Surface vs Hippocampus. J Comp Physiol Psychol 47, 187–193.

Mishkin, M., 1951. Effects of selective ablations of the temporal lobes on the visually guided behavior of monkeys and baboons. 77.

Mishkin, M., Delacour, J., 1975. An analysis of short-term visual memory in the monkey. J Exp Psychol Anim Behav Process 1, 326–334.

Mishkin, M., Pribram, K.H., 1954. Visual Discrimination Performance Following Partial Ablations of the Temporal Lobe: I. Ventral vs Lateral. J Comp Physiol Psychol 47, 14–20.

Miyashita, Y., Rolls, E.T., Cahusac, P.M., Niki, H., Feigenbaum, J.D., 1989. Activity of hippocampal formation neurons in the monkey related to a conditional spatial response task. J. Neurophysiol. 61, 669–678. doi:10.1152/jn.1989.61.3.669

Moll, J.M., 1915. The “Amnestic” or ‘Korsakoff's’ Syndrome, with Alcoholic Etiology: An Analysis of Thirty Cases. Journal of Mental Science 61, 424–443. doi:10.1192/bjp.61.254.424

Moser, E.I., Moser, M.-B., McNaughton, B.L., 2017. Spatial representation in the hippocampal formation: a history. Nat. Neurosci. 20, 1448–1464. doi:10.1038/nn.4653

Muller, R.U., Kubie, J.L., 1987. The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. J. Neurosci. 7, 1951–1968.

Murray, E.A., Mishkin, M., 1983. Severe tactual memory deficits in monkeys after combined removal of the amygdala and hippocampus. Brain Res. 270, 340–344.

Murray, E.A., Wise, S.P., Graham, K.S., 2017. Representational specializations of the hippocampus in phylogenetic perspective. Neurosci. Lett. 680, 4–12. doi:10.1016/j.neulet.2017.04.065

Nadel, L., 1991. The hippocampus and space revisited. Hippocampus 1, 221–229. doi:10.1002/hipo.450010302

Nishijo, H., Ono, T., Eifuku, S., Tamura, R., 1997. The relationship between monkey hippocampus place-related neural activity and action in space. Neurosci. Lett. 226, 57–60.

Nitz, D., McNaughton, B., 2004. Differential modulation of CA1 and dentate gyrus interneurons during exploration of novel environments. J. Neurophysiol. 91, 863–872. doi:10.1152/jn.00614.2003

O'Keefe, J., 1978. The hippocampus as a cognitive map. Oxford University Press, USA.

O'Mara, S.M., Rolls, E.T., Berthoz, A., Kesner, R.P., 1994. Neurons responding to whole-body motion in the primate hippocampus. J. Neurosci. 14, 6511–6523.

Olshausen, B.A., Field, D.J., 1997. Sparse coding with an overcomplete basis set: a strategy employed by V1? Vision Res. 37, 3311–3325.

Ono, T., Eifuku, S., Nakamura, K., Nishijo, H., 1993a. Monkey hippocampal neuron responses related to spatial and non-spatial influence. Neurosci. Lett. 159, 75–78.

Ono, T., Nakamura, K., Fukuda, M., Tamura, R., 1991a. Place recognition responses of neurons in monkey hippocampus. Neurosci. Lett. 121, 194–198.

Ono, T., Nakamura, K., Nishijo, H., Eifuku, S., 1993b. Monkey hippocampal neurons related to spatial and nonspatial functions. J. Neurophysiol. 70, 1516–1529. doi:10.1152/jn.1993.70.4.1516

Ono, T., Tamura, R., Nakamura, K., 1991b. The hippocampus and space: are there “place neurons” in the monkey hippocampus? Hippocampus 1, 253–257. doi:10.1002/hipo.450010309

Orbach, J., Milner, B., Rasmussen, T., 1960. Learning and retention in monkeys after amygdala-hippocampus resection. Arch. Neurol. 3, 230–251.

Parkinson, J.K., Murray, E.A., Mishkin, M., 1988. A selective mnemonic role for the hippocampus in monkeys: memory for the location of objects. J. Neurosci. 8, 4159–4167.

Penfield, W., 1958a. Some mechanisms of consciousness discovered during electrical stimulation of the brain. Proceedings of the National Academy of Sciences 44, 51–66. doi:10.1073/pnas.44.2.51

Penfield, W., 1958b. The Rôle of the Temporal Cortex in Recall of Past Experience and Interpretation of the Present, in: Wolstenholme, G.E.W., O'Conner, C.M. (Eds.), Ciba Foundation Symposium on the Neurological Basis of Behaviour, Ciba/Neurological. John Wiley & Sons, Ltd., Chichester, UK, pp. 149–174. doi:10.1002/9780470719091.ch9

Penfield, W., Milner, B., 1958. Memory deficit produced by bilateral lesions in the hippocampal zone. AMA Arch Neurol Psychiatry 79, 475–497.

Preuss, T.M., 2000. Taking the measure of diversity: comparative alternatives to the model-animal paradigm in cortical neuroscience. Brain Behav. Evol. 55, 287–299. doi:10.1159/000006664

Pribram, K.H., Kruger, L., 1954. Functions of the "olfactory brain". Ann. N. Y. Acad. Sci. 58, 109–138. doi:10.1111/j.1749-6632.1954.tb54849.x

Pribram, K.H., Wilson, W.A., Connors, J., 1962. Effects of lesions of the medial forebrain on alternation behavior of rhesus monkeys. Experimental Neurology 6, 36–47. doi:10.1016/0014-4886(62)90013-4

Ravassard, P., Kees, A., Willers, B., Ho, D., Aharoni, D., Cushman, J., Aghajan, Z.M., Mehta, M.R., 2013. Multisensory control of hippocampal spatiotemporal selectivity. Science 340, 1342–1346. doi:10.1126/science.1232655

Ridley, R.M., Baker, H.F., 1997. Evidence for a specific information processing deficit in monkeys with lesions of the septo-hippocampal system. Cortex 33, 167–176.

Ridley, R.M., Gribble, S., Clark, B., Baker, H.F., Fine, A., 1992. Restoration of learning ability in fornix-transected monkeys after fetal basal forebrain but not fetal hippocampal tissue transplantation. Neuroscience 48, 779–792.

Ridley, R.M., Timothy, C.J., Maclean, C.J., Baker, H.F., 1995. Conditional learning and memory impairments following neurotoxic lesion of the CA1 field of the hippocampus. Neuroscience 67, 263–275.

Rigotti, M., Barak, O., Warden, M.R., Wang, X.-J., Daw, N.D., Miller, E.K., Fusi, S., 2013. The importance of mixed selectivity in complex cognitive tasks. Nature 497, 585–590. doi:10.1038/nature12160

Robertson, R.G., Rolls, E.T., Georges-Fran ois, P., 1998. Spatial view cells in the primate hippocampus: effects of removal of view details. J. Neurophysiol. 79, 1145–1156. doi:10.1152/jn.1998.79.3.1145

Rolls, E.T., 1999. Spatial view cells and the representation of place in the primate hippocampus. Hippocampus 9, 467–480. doi:10.1002/(SICI)1098-1063(1999)9:4<467::AID-HIPO13>3.0.CO;2-F

Rolls, E.T., Miyashita, Y., Cahusac, P.M., Kesner, R.P., Niki, H., Feigenbaum, J.D., Bach, L., 1989. Hippocampal neurons in the monkey with activity related to the place in which a stimulus is shown. J. Neurosci. 9, 1835–1845.

Rolls, E.T., O'Mara, S.M., 1995. View-responsive neurons in the primate hippocampal complex. Hippocampus 5, 409–424. doi:10.1002/hipo.450050504

Rolls, E.T., Robertson, R.G., Georges-François, P., 1997. Spatial view cells in the primate hippocampus. Eur. J. Neurosci. 9, 1789–1794.

Rolls, E.T., Xiang, J.-Z., 2005. Reward-spatial view representations and learning in the primate hippocampus. J. Neurosci. 25, 6167–6174. doi:10.1523/JNEUROSCI.1481-05.2005

Rupniak, N.M., Gaffan, D., 1987. Monkey hippocampus and learning about spatially directed movements. J. Neurosci. 7, 2331–2337.

Schiller, D., Eichenbaum, H., Buffalo, E.A., Davachi, L., Foster, D.J., Leutgeb, S., Ranganath, C., 2015. Memory and Space: Towards an Understanding of the Cognitive Map. J. Neurosci. 35, 13904–13911. doi:10.1523/JNEUROSCI.2618-15.2015

Scoville, W.B., 1954. The limbic lobe in man. J. Neurosurg. 11, 64–66. doi:10.3171/jns.1954.11.1.0064

Scoville, W.B., Correll, R.E., 1973. Memory and the temporal lobe. A review for clinicians. Acta Neurochir (Wien) 28, 251–258.

Scoville, W.B., Milner, B., 1957. Loss of recent memory after bilateral hippocampal lesions. J. Neurol. Neurosurg. Psychiatr. 20, 11–21.

Skaggs, W.E., McNaughton, B.L., Gothard, K.M., Markus, E.J., 1993. An information-theoretic approach to deciphering the hippocampal code, in:. Presented at the Advances in neural information processing systems, pp. 1030–1037.

Sliwa, J., Planté, A., Duhamel, J.-R., Wirth, S., 2016. Independent Neuronal Representation of Facial and Vocal Identity in the Monkey Hippocampus and Inferotemporal Cortex. Cereb. Cortex 26, 950–966. doi:10.1093/cercor/bhu257

Smith, A.C., Frank, L.M., Wirth, S., Yanike, M., Hu, D., Kubota, Y., Graybiel, A.M., Suzuki, W.A., Brown, E.N., 2004. Dynamic analysis of learning in behavioral experiments. J. Neurosci. 24, 447–461. doi:10.1523/JNEUROSCI.2908-03.2004

Squire, L.R., 1992. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychol Rev 99, 195–231.

Squire, L.R. (Ed.), 1998. The History of Neuroscience in Autobiography. The Society for Neuroscience.

Stachenfeld, K.L., Botvinick, M.M., Gershman, S.J., 2017. The hippocampus as a predictive map. Nat. Neurosci. 7, 1951–1653. doi:10.1038/nn.4650

Stefanini, F., Kheirbek, M., Kushnir, L., Jennings, J.H., Stuber, G., Hen, R., Fusi, S., 2018. A distributed neural code in ensembles of dentate gyrus granule cells. bioRxiv. doi:10.1101/292953

Stepien, L.S., Cordeau, J.P., Rasmussen, T., 1960. The Effect of Temporal Lobe and Hippocampal Lesions on Auditory and Visual Recent Memory in Monkeys. Brain 83, 470–489. doi:10.1093/brain/83.3.470

Suthana, N.A., Parikshak, N.N., Ekstrom, A.D., Ison, M.J., Knowlton, B.J., Bookheimer, S.Y., Fried, I., 2015. Specific responses of human hippocampal neurons are associated with better memory. Proc. Natl. Acad. Sci. U.S.A. 112, 10503–10508. doi:10.1073/pnas.1423036112

Suzuki, W.A., 2008. Learning, Memory, and the Monkey Hippocampus, in:. Oxford University Press. doi:10.1093/acprof:oso/9780195323245.003.0016

Tamura, R., Ono, T., Fukuda, M., Nakamura, K., 1990. Recognition of egocentric and allocentric visual and auditory space by neurons in the hippocampus of monkeys. Neurosci. Lett. 109, 293–298. doi:10.1016/0304-3940(90)90010-7

Tamura, R., Ono, T., Fukuda, M., Nishijo, H., 1991. Role of monkey hippocampus in recognition of food and nonfood. Brain Res. Bull. 27, 457–461.

Tank, D.W., Hopfield, J.J., 1987. Collective computation in neuronlike circuits. Sci. Am. 257, 104–114.

Tolman, E.C., 1948. Cognitive maps in rats and men. Psychol Rev 55, 189–208.

Wallace, D.J., Greenberg, D.S., Sawinski, J., Rulla, S., Notaro, G., Kerr, J.N.D., 2013. Rats maintain an overhead binocular field at the expense of constant fusion. Nature 498, 65–69. doi:10.1038/nature12153

Warrington, E.K., Taylor, A.M., 1973. Immediate memory for faces: long- or short-term memory? Q J Exp Psychol 25, 316–322. doi:10.1080/14640747308400352

Watanabe, T., Niki, H., 1985. Hippocampal unit activity and delayed response in the monkey. Brain Res. 325, 241–254. doi:10.1016/0006-8993(85)90320-8

Waxler, M., Enger Rosvold, H., 1970. Delayed alternation in monkeys after removal of the hippocampus. Neuropsychologia 8, 137–146. doi:10.1016/0028-3932(70)90001-1

Wässle, H., Grünert, U., Röhrenbeck, J., Boycott, B.B., 1989. Cortical magnification factor and the ganglion cell density of the primate retina. Nature 341, 643–646. doi:10.1038/341643a0

Wilson, F.A., Riches, I.P., Brown, M.W., 1990. Hippocampus and medial temporal cortex: neuronal activity related to behavioural responses during the performance of memory tasks by primates. Behav. Brain Res. 40, 7–28.

Wilson, M.A., McNaughton, B.L., 1993. Dynamics of the hippocampal ensemble code for space. Science 261, 1055–1058.

Wirth, S., Avsar, E., Chiu, C.C., Sharma, V., Smith, A.C., Brown, E., Suzuki, W.A., 2009. Trial Outcome and Associative Learning Signals in the Monkey Hippocampus. Neuron 61, 930–940. doi:10.1016/j.neuron.2009.01.012

Wirth, S., Baraduc, P., Planté, A., Pinède, S., Duhamel, J.-R., 2017. Gaze-informed, task-situated representation of space in primate hippocampus during virtual navigation. PLoS Biol. 15, e2001045. doi:10.1371/journal.pbio.2001045

Wirth, S., Yanike, M., Frank, L.M., Smith, A.C., Brown, E.N., Suzuki, W.A., 2003. Single neurons in the monkey hippocampus and learning of new associations. Science 300, 1578–1581. doi:10.1126/science.1084324

Xiang, J.Z., Brown, M.W., 1999. Differential neuronal responsiveness in primate perirhinal cortex and hippocampal formation during performance of a conditional visual discrimination task. Eur. J. Neurosci. 11, 3715–3724.

Yokota, T., Reeves, A.G., MacLean, P.D., 1967. Intracellular Olfactory Response of Hippocampal Neurons in Awake, Sitting Squirrel Monkeys. Science 157, 1072–1074. doi:10.1126/science.157.3792.1072

Zola, S.M., Squire, L.R., 2001. Relationship between magnitude of damage to the hippocampus and impaired recognition memory in monkeys. Hippocampus 11, 92–98. doi:10.1002/hipo.1027

Zola-Morgan, S., Squire, L.R., 1985. Medial temporal lesions in monkeys impair memory on a variety of tasks sensitive to human amnesia. Behav. Neurosci. 99, 22–34.

9 APPENDICES

APPENDIX I: COMPLETE BIBLIOGRAPHY OF HIPPOCAMPAL LESION STUDIES IN NON-HUMAN PRIMATES

The following pages contain the citation from what the author believes to be every peer-reviewed experimental study of hippocampal lesion non-human primates published to date. Note, preliminary reports, conference proceedings, review articles, and book chapters that are not primarily research are excluded.

1880s

1. Ferrier, D. (1886). Functions of the Brain. G.P. Putnam's Sons.
2. Brown, S., & Schäfer, E. A. (1888). XI. An investigation into the functions of the occipital and temporal lobes of the monkey's brain. Phil. Trans. R. Soc. Lond. B, 179, 303–327. http://doi.org/10.1098/rstb.1888.0011

1890s

3. Lissauer, H. (1890). Ein Fall von Seelenblindheit nebst einem Beitrage Theorie derselben, Arch. f. Psychiat. 21:222-270.

1930s

4. Jacobsen, C. F., and Elder, J.H. Studies of cerebral function in primates. II. The effect of temporal lobe lesions on delayed response in monkeys. Comp. Psychol. Monogr., 1936, 13, no. 3, 61-65
5. Klüver, H., & Bucy, P. C. (1937). “Psychic Blindness” and Other Symptoms Following Bilateral Temporal Lobectomy in Rhesus Monkeys. American Journal of Physiology, 119, 352–353
6. Klüver, H., & Bucy, P. C. (1938). An Analysis of Certain Effects of Bilateral Temporal Lobectomy in the Rhesus Monkey, with Special Reference to “Psychic Blindness.” The Journal of Psychology, 5(1), 33–54. http://doi.org/10.1080/00223980.1938.9917551
7. Klüver, H., & Bucy, P. C. (1939). Preliminary Analysis of Functions of the Temporal Lobes in Monkeys. Archives of Neurology and Psychiatry, 42(6), 979. http://doi.org/10.1001/archneurpsyc.1939.02270240017001

1940s

8. Malmo, R. B. Interference factors in delayed response in monkeys after removal of frontal lobes. J. Neurophysiol., 1942, 5, 295-508.

1950s

9. Blum, J. S., Chow, K. L., & Pribram, K. H. (1950). A behavioral analysis of the organization of the parieto-temporo-preoccipital cortex. The Journal of Comparative Neurology, 93(1), 53–100.
10. Mishkin M, Pribram KH. Visual discrimination performance following partial ablations of the temporal lobe. I. Ventral vs. lateral. J Comp Physiol Psychol. 1954 Feb;47(1):14-20. PubMed PMID: 13130724.
11. Mishkin M. Visual discrimination performance following partial ablations of the temporal lobe. II. Ventral surface vs. hippocampus. J Comp Physiol Psychol. 1954 Jun;47(3):187-93. PubMed PMID: 13163252.
12. Weiskrantz, L., & Mishkin, M. (1958). Effects of Temporal and Frontal Cortical Lesions on Auditory Discrimination in Monkeys. Brain, 81(3), 406–414. http://doi.org/10.1093/brain/81.3.406

1960s

13. Stepien, L. S., Cordeau, J. P. & Rasmussen, T. (1960). The Effect of Temporal Lobe and Hippocampal Lesions on Auditory and Visual Recent Memory in Monkeys. Brain 83, 470–489.
14. Orbach, J., Milner, B., Rasmussen, T. (1960). Learning and retention in monkeys after amygdala-hippocampus resection. Arch Neurol. Sep;3:230-51. PubMed PMID: 14428979.
15. Kimble, D. P., & Pribram, K. H. (1963). Hippocampectomy and behavior sequences. Science (New York, N.Y.), 139(3557), 824–825.
16. Walker, A. E., Thomson, A. F., and J. D. McQueen. 1963. Behavior and temporal rhinencephalon in the monkey. Bull. Johns Hopkins Hosp. 93: 65-93.
17. Gol, A., Kellaway, P., Shapiro, M., & Hurst, C. M. (1963). Studies of Hippocampectomy in the Monkey, Baboon, and Cat. Behavioral Changes and a Preliminary Evaluation of Cognitive Function. Neurology, 13, 1031–1041.
18. Mahut, H., & Cordeau, J.-P. (1963). Spatial reversal deficit in monkeys with amygdalohippocampal ablations. Experimental Neurology, 7(5), 426–434. http://doi.org/10.1016/0014-4886(63)90023-2

19. Cordeau, J. P., & Mahut, H. (1964). Some Long–Term Effects of Temporal Lobe Resections on Auditory and Visual Discrimination in Monkeys. Brain, 87(1), 177–190. http://doi.org/10.1093/brain/87.1.177
20. Drachman, D. A., & Ommaya, A. K. (1964). Memory and the Hippocampal Complex. Archives of Neurology, 10(4), 411–425. http://doi.org/10.1001/archneur.1964.00460160081008
21. Shapiro, M. M., Gol, A., & Kellaway, P. (1965). Acquisition, retention, and discrimination reversal after hippocampal ablation in monkeys. Experimental Neurology, 13(2), 128–144.
22. Correll, R. E., & Scoville, W. B. (1965a). Effects of medial temporal lesions on visual discrimination performance. Journal of Comparative and Physiological Psychology, 60(2), 175–181.
23. Correll, R. E., & Scoville, W. B. (1965b). Performance on delayed match following lesions of medial temporal lobe structures. Journal of Comparative and Physiological Psychology, 60(3), 360–367.
24. Correll, R. E., & Scoville, W. B. (1967). Significance of delay in the performance of monkeys with medial temporal lobe resections. Experimental Brain Research, 4(1), 85–96.

1970s

25. Correll, R. E., & Scoville, W. B. (1970). Relationship of ITI to acquistion of serial visual discriminations following temporal rhinencephalic resection in monkeys. Journal of Comparative and Physiological Psychology, 70(3), 464–469.
26. Waxler, M., & Enger Rosvold, H. (1970). Delayed alternation in monkeys after removal of the hippocampus. Neuropsychologia, 8(2), 137–146. http://doi.org/10.1016/0028-3932(70)90001-1
27. Jackson FB, Gergen JA. Acquisition of operant schedules by squirrel monkeys lesioned in the hippocampal area. Physiol Behav. 1970 May;5(5):543-7. PubMed PMID: 5535509.
28. Mahut H. Spatial and object reversal learning in monkeys with partial temporal lobe ablations. Neuropsychologia. 1971 Dec;9(4):409-24. PubMed PMID: 5005998.
29. Mahut, H. (1972). A selective spatial deficit in monkeys after transection of the fornix. Neuropsychologia, 10(1), 65–74. http://doi.org/10.1016/0028-3932(72)90043-7
30. Jones B, Mishkin M. Limbic lesions and the problem of stimulus—reinforcement associations. Exp Neurol. 1972 Aug;36(2):362-77. PubMed PMID: 4626489.

31. Mahut, H., & Zola, S. M. (1973). A non-modality specific impairment in spatial learning after fornix lesions in monkeys. Neuropsychologia, 11(3), 255–269. http://doi.org/10.1016/0028-3932(73)90037-7.
32. Zola SM, Mahut H. Paradoxical facilitation of object reversal learning after transection of the fornix in monkeys. Neuropsychologia. 1973 Jul;11(3):271-84. PubMed PMID: 4792178.
33. Gaffan D. Recognition impaired and association intact in the memory of monkeys after transection of the fornix. J Comp Physiol Psychol. 1974 Jun;86(6):1100-9. PubMed PMID: 4209603.
34. Horel JA, Misantone LJ. Visual discrimination impaired by cutting temporal lobe connections. Science. 1976 Jul 23;193(4250):336-8. PubMed PMID: 819992.
35. Gaffan D. Monkeys' recognition memory for complex pictures and the effect of fornix transection. Q J Exp Psychol. 1977 Aug;29(3):505-14. PubMed PMID: 410065.
36. Gaffan D. Recognition memory after short retention intervals in fornix-transected monkeys. Q J Exp Psychol. 1977 Nov;29(4):577-88. PubMed PMID:414291.
37. Mishkin M. Memory in monkeys severely impaired by combined but not by separate removal of amygdala and hippocampus. Nature. 1978 May 25;273(5660):297-8. PubMed PMID: 418358.
38. Jackson, W. J., & Regestein, Q. R. (1979). Hippocampal lesions impair prolonged titrated avoidance by rhesus monkeys. Experimental Neurology, 63(1), 28–34.

1980s

39. Gaffan D, Weiskrantz L. Recency effects and lesion effects in delayed non-matching to randomly baited samples by monkeys. Brain Res. 1980 Sep 8;196(2):373-86. PubMed PMID: 6772278.
40. Mahut H, Moss M, Zola-Morgan S. Retention deficits after combined amygdalo-hippocampal and selective hippocampal resections in the monkey. Neuropsychologia. 1981;19(2):201-25. PubMed PMID: 7254500.
41. Moss M, Mahut H, Zola-Morgan S. Concurrent discrimination learning of monkeys after hippocampal, entorhinal, or fornix lesions. J Neurosci. 1981 Mar;1(3):227-40. PubMed PMID: 7264718.
42. Owen, M.J. and S.R. Butler 9 1981. Amnesia after transection of the fornix in monkeys: Long-term memory impaired, short-term memory intact. Behav. Brain Res. 3: 115.

43. Spiegler BJ, Mishkin M. Evidence for the sequential participation of inferior temporal cortex and amygdala in the acquisition of stimulus-reward associations. Behav Brain Res. 1981 Nov;3(3):303-17. PubMed PMID: 7306385.
44. Mahut H, Zola-Morgan S, Moss M. Hippocampal resections impair associative learning and recognition memory in the monkey. J Neurosci. 1982 Sep;2(9):1214-20. PubMed PMID: 7119874.
45. Zola-Morgan S, Squire LR, Mishkin M. The neuroanatomy of amnesia: amygdala-hippocampus versus temporal stem. Science. 1982 Dec 24;218(4579):1337-9. PubMed PMID: 6890713.
46. Gaffan D, Bolton J. Learning of object-object associations by monkeys. Q J Exp Psychol B. 1983 May;35 (Pt 2):149-55. PubMed PMID: 6683419.
47. Zola-Morgan S, Dabrowska J, Moss M, Mahut H. Enhanced preference for perceptual novelty in the monkey after section of the fornix but not after ablation of the hippocampus. Neuropsychologia. 1983;21(5):433-54. PubMed PMID: 6646398.
48. Murray EA, Mishkin M. Severe tactual memory deficits in monkeys after combined removal of the amygdala and hippocampus. Brain Res. 1983 Jul 4;270(2):340-4. PubMed PMID: 6883103.
49. Saunders RC, Murray EA, Mishkin M. Further evidence that amygdala and hippocampus contribute equally to recognition memory. Neuropsychologia. 1984;22(6):785-96. PubMed PMID: 6527768.
50. Jackson WJ. Regional hippocampal lesions alter matching by monkeys: an anorexiant effect. Physiol Behav. 1984 Apr;32(4):593-601. PubMed PMID: 6148759.
51. Zola-Morgan S, Squire LR. Preserved learning in monkeys with medial temporal lesions: sparing of motor and cognitive skills. J Neurosci. 1984 Apr;4(4):1072-85. PubMed PMID: 6538901.
52. Gaffan D, Gowling EA. Recall of the goal box in latent learning and latent discrimination. Q J Exp Psychol B. 1984 Feb;36(1):39-51. PubMed PMID: 6538691.
53. Gaffan D, Saunders RC, Gaffan EA, Harrison S, Shields C, Owen MJ. Effects of fornix transection upon associative memory in monkeys: role of the hippocampus in learned action. Q J Exp Psychol B. 1984 Aug;36(3):173-221. PubMed PMID: 6541361.
54. Gaffan D, Harrison S. Reversal learning by fornix-transected monkeys. Q J Exp Psychol B. 1984 Aug;36(3):223-34. PubMed PMID: 6541362.

55. Gaffan D, Shields C, Harrison S. Delayed matching by fornix-transected monkeys: the sample, the push and the bait. Q J Exp Psychol B. 1984 Nov;36(4):305-17. PubMed PMID: 6542686.
56. Gaffan D, Gaffan EA, Harrison S. Effects of fornix transection on spontaneous and trained non-matching by monkeys. Q J Exp Psychol B. 1984 Nov;36(4):285-303. PubMed PMID: 6542685.
57. Murray EA, Mishkin M. Severe tactual as well as visual memory deficits follow combined removal of the amygdala and hippocampus in monkeys. J Neurosci. 1984 Oct;4(10):2565-80. PubMed PMID: 6491723.
58. Malamut BL, Saunders RC, Mishkin M. Monkeys with combined amygdalo-hippocampal lesions succeed in object discrimination learning despite 24-hour intertrial intervals. Behav Neurosci. 1984 Oct;98(5):759-69. PubMed PMID: 6487412.
59. Owen MJ, Butler SR. Does amnesia after transection of the fornix in monkeys reflect abnormal sensitivity to proactive interference? Behav Brain Res. 1984 Dec;14(3):183-92. PubMed PMID: 6441587.
60. Aggleton JP, Mishkin M. Mamillary-body lesions and visual recognition in monkeys. Exp Brain Res. 1985;58(1):190-7. PubMed PMID: 3921394.
61. Bachevalier J, Saunders RC, Mishkin M. Visual recognition in monkeys: effects of transection of fornix. Exp Brain Res. 1985;57(3):547-53. PubMed PMID: 3979496.
62. Bachevalier J, Parkinson JK, Mishkin M. Visual recognition in monkeys: effects of separate vs. combined transection of fornix and amygdalofugal pathways. Exp Brain Res. 1985;57(3):554-61. PubMed PMID: 3979497.
63. Zola-Morgan S, Squire LR. Medial temporal lesions in monkeys impair memory on a variety of tasks sensitive to human amnesia. Behav Neurosci. 1985 Feb;99(1):22-34. PubMed PMID: 4041230.
64. Gaffan D. Hippocampus: memory, habit and voluntary movement. Philos Trans R Soc Lond B Biol Sci. 1985 Feb 13;308(1135):87-99. PubMed PMID: 2858877.
65. Gaffan D, Saunders RC. Running recognition of configural stimuli by fornix-transected monkeys. Q J Exp Psychol B. 1985 Feb;37(1):61-71. PubMed PMID:3983421.
66. Zola-Morgan S, Squire LR. Memory impairment in monkeys following lesions limited to the hippocampus. Behav Neurosci. 1986 Apr;100(2):155-60. PubMed PMID: 3964416.
67. Murray EA, Mishkin M. Visual recognition in monkeys following rhinal cortical ablations combined with either amygdalectomy or hippocampectomy. J Neurosci. 1986 Jul;6(7):1991-2003. PubMed PMID: 3734871.

68. Staubli U, Fraser D, Kessler M, Lynch G. Studies on retrograde and anterograde amnesia of olfactory memory after denervation of the hippocampus by entorhinal cortex lesions. Behav Neural Biol. 1986 Nov;46(3):432-44. PubMed PMID: 3814047.
69. Brown MW, Wilson FA, Riches IP. Neuronal evidence that inferomedial temporal cortex is more important than hippocampus in certain processes underlying recognition memory. Brain Res. 1987 Apr 14;409(1):158-62. PubMed PMID: 3107754.
70. Rupniak NM, Gaffan D. Monkey hippocampus and learning about spatially directed movements. J Neurosci. 1987 Aug;7(8):2331-7. PubMed PMID: 3612244.
71. Parkinson JK, Murray EA, Mishkin M. A selective mnemonic role for the hippocampus in monkeys: memory for the location of objects. J Neurosci. 1988 Nov;8(11):4159-67. PubMed PMID: 3183716.
72. Ringo JL. Seemingly discrepant data from hippocampectomized macaques are reconciled by detectability analysis. Behav Neurosci. 1988 Feb;102(1):173-7. PubMed PMID: 3355654.
73. Phillips RR, Malamut BL, Bachevalier J, Mishkin M. Dissociation of the effects of inferior temporal and limbic lesions on object discrimination learning with 24-h intertrial intervals. Behav Brain Res. 1988 Feb;27(2):99-107. PubMed PMID: 3358857.
74. Raffaele KC, Olton DS. Hippocampal and amygdaloid involvement in working memory for nonspatial stimuli. Behav Neurosci. 1988 Jun;102(3):349-55. PubMed PMID: 3395446.
75. Paller KA, Zola-Morgan S, Squire LR, Hillyard SA. P3-like brain waves in normal monkeys and in monkeys with medial temporal lesions. Behav Neurosci. 1988 Oct;102(5):714-25. PubMed PMID: 3196441.
76. Gaffan D, Harrison S. A comparison of the effects of fornix transection and sulcus principalis ablation upon spatial learning by monkeys. Behav Brain Res. 1989 Jan 1;31(3):207-20. PubMed PMID: 2914072.
77. Gaffan D, Harrison S. Place memory and scene memory: effects of fornix transection in the monkey. Exp Brain Res. 1989;74(1):202-12. PubMed PMID:2924836.
78. Bachevalier J, Mishkin M. Mnemonic and neuropathological effects of occluding the posterior cerebral artery in Macaca mulatta. Neuropsychologia. 1989;27(1):83-105. PubMed PMID: 2710318.
79. Murray EA, Davidson M, Gaffan D, Olton DS, Suomi S. Effects of fornix transection and cingulate cortical ablation on spatial memory in rhesus monkeys. Exp Brain Res. 1989;74(1):173-86. PubMed PMID: 2924834.

80. Uno H, Tarara R, Else JG, Suleman MA, Sapolsky RM. Hippocampal damage associated with prolonged and fatal stress in primates. J Neurosci. 1989 May;9(5):1705-11. PubMed PMID: 2723746.
81. Zola-Morgan S, Squire LR, Amaral DG. Lesions of the hippocampal formation but not lesions of the fornix or the mammillary nuclei produce long-lasting memory impairment in monkeys. J Neurosci. 1989 Mar;9(3):898-913. PubMed PMID: 2494309.
82. Zola-Morgan S, Squire LR, Amaral DG. Lesions of the amygdala that spare adjacent cortical regions do not impair memory or exacerbate the impairment following lesions of the hippocampal formation. J Neurosci. 1989 Jun;9(6):1922-36. PubMed PMID: 2723757.
83. Zola-Morgan S, Squire LR, Amaral DG, Suzuki WA (1989) Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. J Neurosci 9:43554370.
84. Diamond A, Zola-Morgan S, Squire LR. Successful performance by monkeys with lesions of the hippocampal formation on AB and object retrieval, two tasks that mark developmental changes in human infants. Behav Neurosci. 1989 Jun;103(3):526-37. PubMed PMID: 2736067.
85. Cirillo RA, Horel JA, George PJ. Lesions of the anterior temporal stem and the performance of delayed match-to-sample and visual discriminations in monkeys. Behav Brain Res. 1989 Aug 1;34(1-2):55-69. PubMed PMID: 2765172.
86. George PJ, Horel JA, Cirillo RA. Reversible cold lesions of the parahippocampal gyrus in monkeys result in deficits on the delayed match-to-sample and other visual tasks. Behav Brain Res. 1989 Sep 1;34(3):163-78. PubMed PMID: 2789698.
87. Saunders RC, Weiskrantz L. The effects of fornix transection and combined fornix transection, mammillary body lesions and hippocampal ablations on object-pair association memory in the rhesus monkey. Behav Brain Res. 1989 Nov 1;35(2):85-94. PubMed PMID: 2510765.
88. Zola-Morgan S, Squire LR, Amaral DG, Suzuki WA. Lesions of perirhinal and parahippocampal cortex that spare the amygdala and hippocampal formation produce severe memory impairment. J Neurosci. 1989 Dec;9(12):4355-70. PubMed PMID: 2593004.

1990s

89. Overman WH, Ormsby G, Mishkin M. Picture recognition vs. picture discrimination learning in monkeys with medial temporal removals. Exp Brain Res. 1990;79(1):18-24. PubMed PMID: 2311695.
90. Irle E, Markowitsch HJ. Functional recovery after limbic lesions in monkeys. Brain Res Bull. 1990 Jul;25(1):79-92. PubMed PMID: 2207719.
91. Kordower JH, Fiandaca MS. Response of the monkey cholinergic septohippocampal system to fornix transection: a histochemical and cytochemical analysis. J Comp Neurol. 1990 Aug 22;298(4):443-57. PubMed PMID: 2172323.
92. Zola-Morgan SM, Squire LR. The primate hippocampal formation: evidence for a time-limited role in memory storage. Science. 1990 Oct 12;250(4978):288-90. PubMed PMID: 2218534.
93. Bachevalier J, Brickson M, Hagger C, Mishkin M. Age and sex differences in the effects of selective temporal lobe lesion on the formation of visual discrimination habits in rhesus monkeys (Macaca mulatta). Behav Neurosci. 1990 Dec;104(6):885-99. PubMed PMID: 2285487.
94. Zola-Morgan S, Squire LR, Alvarez-Royo P, Clower RP. Independence of memory functions and emotional behavior: separate contributions of the hippocampal formation and the amygdala. Hippocampus. 1991 Apr;1(2):207-20. PubMed PMID: 1669294.
95. Gaffan D, Lim C. Hippocampus and the blood supply to TE: parahippocampal pial section impairs visual discrimination learning in monkeys. Exp Brain Res. 1991;87(1):227-31. PubMed PMID: 1756830.
96. Squire LR, Zola-Morgan S. The medial temporal lobe memory system. Science 1991; 253: 1380.
97. Gaffan EA, Gaffan D, Hodges JR. Amnesia following damage to the left fornix and to other sites. A comparative study. Brain. 1991 Jun;114 (Pt 3):1297-313. PubMed PMID: 2065251.
98. Gaffan D, Watkins S. Mediodorsal Thalamic Lesions Impair Long-Term Visual Associative Memory in Macaques. Eur J Neurosci. 1991 Jul;3(7):615-620. PubMed PMID: 12106469.
99. Gaffan D, Harrison S. Auditory-visual associations, hemispheric specialization and temporal-frontal interaction in the rhesus monkey. Brain. 1991 Oct;114 (Pt 5):2133-44. PubMed PMID: 1933238.

100. Samson Y, Friedman AH, Wu JJ, Davis JN. Loss of hippocampal acetylcholinesterase staining after fornix lesion in the monkey. Exp Neurol. 1991 Oct;114(1):123-31. PubMed PMID: 1717308.

101. Gaffan D, Murray EA. Monkeys (Macaca fascicularis) with rhinal cortex ablations succeed in object discrimination learning despite 24-hr intertrial intervals and fail at matching to sample despite double sample presentations. Behav Neurosci. 1992 Feb;106(1):30-8. PubMed PMID: 1554436.

102. Ridley RM, Gribble S, Clark B, Baker HF, Fine A. Restoration of learning ability in fornix-transected monkeys after fetal basal forebrain but not fetal hippocampal tissue transplantation. Neuroscience. 1992 Jun;48(4):779-92. PubMed PMID: 1630624.

103. Zola-Morgan S, Squire LR, Rempel NL, Clower RP, Amaral DG. Enduring memory impairment in monkeys after ischemic damage to the hippocampus. J Neurosci. 1992 Jul;12(7):2582-96. PubMed PMID: 1613549.

104. Scheller MS, Grafe MR, Zornow MH, Fleischer JE. Effects of ischemia duration on neurological outcome, CA1 histopathology, and nonmatching to sample learning in monkeys. Stroke. 1992 Oct;23(10):1471-6; discussion 1477-8. PubMed PMID: 1412584.

105. Alvarez-Royo P, Zola-Morgan S, Squire LR. Impairment of long-term memory and sparing of short-term memory in monkeys with medial temporal lobe lesions: a response to Ringo. Behav Brain Res. 1992 Nov 30;52(1):1-5. PubMed PMID: 1472284.

106. Zola-Morgan S, Squire LR, Clower RP, Rempel NL. Damage to the perirhinal cortex exacerbates memory impairment following lesions to the hippocampal formation. J Neurosci. 1993 Jan;13(1):251-65. PubMed PMID: 8423472.

107. Gaffan D. Normal forgetting, impaired acquisition in memory for complex naturalistic scenes by fornix-transected monkeys. Neuropsychologia. 1993 Apr;31(4):403-6. PubMed PMID: 8502375.

108. Gaffan D. Additive effects of forgetting and fornix transfection in the temporal gradient of retrograde amnesia. Neuropsychologia. 1993 Oct;31(10):1055-66. PubMed PMID: 8290022.

109. Angeli SJ, Murray EA, Mishkin M. Hippocampectomized monkeys can remember one place but not two. Neuropsychologia. 1993 Oct;31(10):1021-30. PubMed PMID:8290020.

110. Murray EA, Gaffan D, Mishkin M. Neural substrates of visual stimulus-stimulus association in rhesus monkeys. J Neurosci. 1993 Oct;13(10):4549-61. PubMed PMID: 8410203.

111. Salzmann E, Vidyasagar TR, Creutzfeldt OD. Functional comparison of neuronal properties in the primate posterior hippocampus and parahippocampus (area TF/TH) during different behavioural paradigms involving memory and selective attention. Behav Brain Res. 1993 Feb 26;53(1-2):133-49. PubMed PMID: 8466659.

112. Baylis GC, Moore BO. Hippocampal lesions impair spatial response selection in the primate. Exp Brain Res. 1994;98(1):110-8. PubMed PMID: 8013578.

113. Alvarez P, Zola-Morgan S, Squire LR. The animal model of human amnesia: long-term memory impaired and short-term memory intact. Proc Natl Acad Sci U S A. 1994 Jun 7;91(12):5637-41. PubMed PMID: 8202540; PubMed Central PMCID: PMC44051.

114. Zola-Morgan S, Squire LR, Ramus SJ. Severity of memory impairment in monkeys as a function of locus and extent of damage within the medial temporal lobe memory system. Hippocampus. 1994 Aug;4(4):483-95. PubMed PMID: 7874239.

115. Gaffan D. Dissociated effects of perirhinal cortex ablation, fornix transection and amygdalectomy: evidence for multiple memory systems in the primate temporal lobe. Exp Brain Res. 1994;99(3):411-22. PubMed PMID: 7957720.

116. Gaffan D. Scene-specific memory for objects: a model of episodic memory impairment in monkeys with fornix transection. J Cogn Neurosci. 1994 Fall;6(4):305-20. doi: 10.1162/jocn.1994.6.4.305. PubMed PMID: 23961727.

117. Málková L, Mishkin M, Bachevalier J. Long-term effects of selective neonatal temporal lobe lesions on learning and memory in monkeys. Behav Neurosci. 1995 Apr;109(2):212-26. PubMed PMID: 7619312.

118. Ridley RM, Timothy CJ, Maclean CJ, Baker HF. Conditional learning and memory impairments following neurotoxic lesion of the CA1 field of the hippocampus. Neuroscience. 1995 Jul;67(2):263-75. PubMed PMID: 7675168.

119. Leonard BW, Amaral DG, Squire LR, Zola-Morgan S. Transient memory impairment in monkeys with bilateral lesions of the entorhinal cortex. J Neurosci. 1995 Aug;15(8):5637-59. PubMed PMID: 7643207.

120. Beauregard M, Malkova L, Bachevalier J. Stereotypies and loss of social affiliation after early hippocampectomy in primates. Neuroreport. 1995 Dec 15;6(18):2521-6. PubMed PMID: 8741754.

121. Ridley RM, Baker HF, Harder JA, Pearson C. Effects of lesions of different parts of the septo-hippocampal system in primates on learning and retention of information acquired before or after surgery. Brain Res Bull. 1996;40(1):21-32. PubMed PMID: 8722749.

122. Meunier M, Hadfield W, Bachevalier J, Murray EA. Effects of rhinal cortex lesions combined with hippocampectomy on visual recognition memory in rhesus monkeys. J Neurophysiol. 1996 Mar;75(3):1190-205. PubMed PMID: 8867128.

123. Baylis GC, Moore BO. Hippocampal lesions cause forgetting in a spatial response task. Eur J Neurosci. 1996 May;8(5):853-60. PubMed PMID: 8743733.

124. Gaffan D, Parker A. Interaction of perirhinal cortex with the fornix-fimbria: memory for objects and "object-in-place" memory. J Neurosci. 1996 Sep 15;16(18):5864-9. PubMed PMID: 8795638.

125. Murray EA, Wise SP. Role of the hippocampus plus subjacent cortex but not amygdala in visuomotor conditional learning in rhesus monkeys. Behav Neurosci. 1996 Dec;110(6):1261-70. PubMed PMID: 8986330.

126. Ridley RM, Baker HF. Evidence for a specific information processing deficit in monkeys with lesions of the septo-hippocampal system. Cortex. 1997 Mar;33(1):167-76. PubMed PMID: 9088729.

127. Ridley RM, Pearson C, Kershaw TR, Hodges H, Maclean CJ, Hoyle C, Baker HF. Learning impairment induced by lesion of the CA1 field of the primate hippocampus: attempts to ameliorate the impairment by transplantation of fetal CA1 tissue. Exp Brain Res. 1997 Jun;115(1):83-94. PubMed PMID: 9224836.

128. Parker A, Gaffan D. Mamillary Body Lesions in Monkeys Impair Object-in-Place Memory: Functional Unity of the Fornix-Mamillary System. J Cogn Neurosci. 1997 Jul;9(4):512-21. doi: 10.1162/jocn.1997.9.4.512. PubMed PMID: 23968214.

129. Reed JM, Squire LR. Impaired recognition memory in patients with lesions limited to the hippocampal formation. Behav Neurosci. 1997 Aug;111(4):667-75. PubMed PMID: 9267644.

130. Vargha-Khadem F, Gadian DG, Watkins KE, Connelly A, Van Paesschen W, Mishkin M. Differential effects of early hippocampal pathology on episodic and semantic memory. Science. 1997 Jul 18;277(5324):376-80. Erratum in: Science 1997 Aug 22; 277(5329):1117. PubMed PMID: 9219696.

131. Parker A, Gaffan D. Mamillary Body Lesions in Monkeys Impair Object-in-Place Memory: Functional Unity of the Fornix-Mamillary System. J Cogn Neurosci. 1997 Jul;9(4):512-21. doi: 10.1162/jocn.1997.9.4.512. PubMed PMID: 23968214.

132. Gaffan D. Episodic and semantic memory and the role of the not-hippocampus. Trends Cogn Sci. 1997 Oct;1(7):246-8. doi: 10.1016/S1364-6613(97)01074-7. PubMed PMID: 21223918.

133. Dor© FY, Thornton JA, White NM, Murray EA. Selective hippocampal lesions yield nonspatial memory impairments in rhesus monkeys. Hippocampus. 1998;8(4):323-9. PubMed PMID: 9744419.

134. Goulet S, Dor© FY, Murray EA. Aspiration lesions of the amygdala disrupt the rhinal corticothalamic projection system in rhesus monkeys. Exp Brain Res. 1998 Mar;119(2):131-40. PubMed PMID: 9535562.

135. Buckley MJ, Gaffan D. Perirhinal cortex ablation impairs configural learning and paired-associate learning equally. Neuropsychologia. 1998 Jun;36(6):535-46. PubMed PMID: 9705064.

136. Murray EA, Mishkin M. Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. J Neurosci. 1998 Aug 15;18(16):6568-82. PubMed PMID: 9698344.

137. Parker A, Wilding E, Akerman C. The Von Restorff effect in visual object recognition memory in humans and monkeys. The role of frontal/perirhinal interaction. J Cogn Neurosci. 1998 Nov;10(6):691-703. PubMed PMID: 9831738.

138. Murray EA, Baxter MG, Gaffan D. Monkeys with rhinal cortex damage or neurotoxic hippocampal lesions are impaired on spatial scene learning and object reversals. Behav Neurosci. 1998 Dec;112(6):1291-303. PubMed PMID: 9926813.

139. Buffalo, E. A., Ramus, S. J., Clark, R. E., Teng, E., Squire, L. R., & Zola, S. M. (1999). Dissociation between the effects of damage to perirhinal cortex and area TE. Learning & Memory, 6(6), 572–599. http://doi.org/10.1101/lm.6.6.572

140. Beason-Held LL, Rosene DL, Killiany RJ, Moss MB. Hippocampal formation lesions produce memory impairment in the rhesus monkey. Hippocampus. 1999;9(5):562-74. PubMed PMID: 10560927.

141. Pascalis O, Bachevalier J. Neonatal aspiration lesions of the hippocampal formation impair visual recognition memory when assessed by paired-comparison task but not by delayed nonmatching-to-sample task. Hippocampus. 1999;9(6):609-16. PubMed PMID: 10641753.

142. Ridley RM, Pugh P, Maclean CJ, Baker HF. Severe learning impairment caused by combined immunotoxic lesion of the cholinergic projections to the cortex and hippocampus in monkeys. Brain Res. 1999 Jul 31;836(1-2):120-38. PubMed PMID: 10415411.

2000s

143. Barefoot HC, Baker HF, Ridley RM. Synergistic effects of unilateral immunolesions of the cholinergic projections from the basal forebrain and contralateral ablations of the inferotemporal cortex and hippocampus in monkeys. Neuroscience. 2000;98(2):243-51. PubMed PMID: 10854755.

144. Zola SM, Squire LR, Teng E, Stefanacci L, Buffalo EA, Clark RE. Impaired recognition memory in monkeys after damage limited to the hippocampal region. J Neurosci. 2000 Jan 1;20(1):451-63. PubMed PMID: 10627621.

145. Loftus M, Knight RT, Amaral DG. An analysis of atrophy in the medial mammillary nucleus following hippocampal and fornix lesions in humans and nonhuman primates. Exp Neurol. 2000 May;163(1):180-90. PubMed PMID: 10785457.

146. Teng E, Stefanacci L, Squire LR, Zola SM. Contrasting effects on discrimination learning after hippocampal lesions and conjoint hippocampal-caudate lesions in monkeys. J Neurosci. 2000 May 15;20(10):3853-63. PubMed PMID: 10804225.

147. Manns JR, Stark CE, Squire LR. The visual paired-comparison task as a measure of declarative memory. Proc Natl Acad Sci U S A. 2000 Oct 24;97(22):12375-9. PubMed PMID: 11027310; PubMed Central PMCID: PMC17349.

148. Ridley RM, Hardy A, Maclean CJ, Baker HF. Non-spatial acquisition and retention deficits following small excitotoxic lesions within the hippocampus in monkeys. Neuroscience. 2001;107(2):239-48. PubMed PMID: 11731098.

149. Gaffan D, Parker A, Easton A. Dense amnesia in the monkey after transection of fornix, amygdala and anterior temporal stem. Neuropsychologia. 2001;39(1):51-70. PubMed PMID: 11115655.

150. Baxter MG, Murray EA. Opposite relationship of hippocampal and rhinal cortex damage to delayed nonmatching-to-sample deficits in monkeys. Hippocampus. 2001;11(1):61-71. PubMed PMID: 11261774.

151. Baxter MG, Murray EA. Effects of hippocampal lesions on delayed nonmatching-to-sample in monkeys: a reply to Zola and Squire (2001). Hippocampus. 2001;11(3):201-3. PubMed PMID: 11769304.

152. Maclean CJ, Gaffan D, Baker HF, Ridley RM. Visual discrimination learning impairments produced by combined transections of the anterior temporal stem, amygdala and fornix in marmoset monkeys. Brain Res. 2001 Jan 5;888(1):34-50. PubMed PMID: 11146050.

153. Ridley RM, Warner KA, Maclean CJ, Gaffan D, Baker HF. Visual agnosia and Kluver-Bucy syndrome in marmosets (Callithrix jacchus) following ablation of

inferotemporal cortex, with additional mnemonic effects of immunotoxic lesions of cholinergic projections to medial temporal areas. Brain Res. 2001 Apr 13;898(1):136-51. PubMed PMID: 11292457.

154. Maguire EA, Vargha-Khadem F, Mishkin M. The effects of bilateral hippocampal damage on fMRI regional activations and interactions during memory retrieval. Brain. 2001 Jun;124(Pt 6):1156-70. PubMed PMID: 11353732.

155. Düzel E, Vargha-Khadem F, Heinze HJ, Mishkin M. Brain activity evidence for recognition without recollection after early hippocampal damage. Proc Natl Acad Sci U S A. 2001 Jul 3;98(14):8101-6. PubMed PMID: 11438748; PubMed Central PMCID: PMC35474.

156. Alvarado MC, Wright AA, Bachevalier J. Object and spatial relational memory in adult rhesus monkeys is impaired by neonatal lesions of the hippocampal formation but not the amygdaloid complex. Hippocampus. 2002;12(4):421-33. PubMed PMID: 12201627.

157. Barefoot HC, Baker HF, Ridley RM. Crossed unilateral lesions of temporal lobe structures and cholinergic cell bodies impair visual conditional and object discrimination learning in monkeys. Eur J Neurosci. 2002 Feb;15(3):507-16. PubMed PMID: 11876778.

158. Easton A, Ridley RM, Baker HF, Gaffan D. Unilateral lesions of the cholinergic basal forebrain and fornix in one hemisphere and inferior temporal cortex in the opposite hemisphere produce severe learning impairments in rhesus monkeys. Cereb Cortex. 2002 Jul;12(7):729-36. PubMed PMID: 12050084.

159. Petrulis A, Eichenbaum H. The perirhinal-entorhinal cortex, but not the hippocampus, is critical for expression of individual recognition in the context of the Coolidge effect. Neuroscience. 2003;122(3):599-607. PubMed PMID: 14622903.

160. Malkova L, Mishkin M. One-trial memory for object-place associations after separate lesions of hippocampus and posterior parahippocampal region in the monkey. J Neurosci. 2003 Mar 1;23(5):1956-65. PubMed PMID: 12629201.

161. Barefoot HC, Maclean CJ, Baker HF, Ridley RM. Unilateral hippocampal and inferotemporal cortex lesions in opposite hemispheres impair learning of single-pair visual discriminations as well as visuovisual conditional tasks in monkeys. Behav Brain Res. 2003 Apr 17;141(1):51-62. PubMed PMID: 12672559.

162. Nemanic S, Alvarado MC, Bachevalier J. The hippocampal/parahippocampal regions and recognition memory: insights from visual paired comparison versus object-

delayed nonmatching in monkeys. J Neurosci. 2004 Feb 25;24(8):2013-26. PubMed PMID: 14985444.

163. Bauman MD, Lavenex P, Mason WA, Capitanio JP, Amaral DG. The development of social behavior following neonatal amygdala lesions in rhesus monkeys. J Cogn Neurosci. 2004 Oct;16(8):1388-411. PubMed PMID: 15509386.

164. Buckmaster CA, Eichenbaum H, Amaral DG, Suzuki WA, Rapp PR. Entorhinal cortex lesions disrupt the relational organization of memory in monkeys. J Neurosci. 2004 Nov 3;24(44):9811-25. PubMed PMID: 15525766.

165. Rehbein L, Killiany R, Mahut H. Developmental study of the hippocampal formation in rhesus monkeys (Macaca mulatta): I. Early ablations spare discrimination learning but not recognition memory. Behav Neurosci. 2005 Jun;119(3):635-50. PubMed PMID: 15998185

166. Killiany R, Rehbein L, Mahut H. Developmental study of the hippocampal formation in rhesus monkeys (Macaca mulatta): II. Early ablations do not spare the capacity to retrieve conditional object-object associations. Behav Neurosci. 2005 Jun;119(3) 651-61. PubMed PMID: 15998186.

167. Belcher AM, Harrington RA, Malkova L, Mishkin M. Effects of hippocampal lesions on the monkey's ability to learn large sets of object-place associations. Hippocampus. 2006;16(4):361-7. PubMed PMID: 16358315.

168. Kwok SC, Buckley MJ. Fornix transection impairs exploration but not locomotion in ambulatory macaque monkeys. Hippocampus. 2006;16(8):655-63. PubMed PMID: 16779812.

169. Lavenex PB, Amaral DG, Lavenex P. Hippocampal lesion prevents spatial relational learning in adult macaque monkeys. J Neurosci. 2006 Apr 26;26(17):4546-58. PubMed PMID: 16641234.

170. Goursaud AP, Bachevalier J. Social attachment in juvenile monkeys with neonatal lesion of the hippocampus, amygdala and orbital frontal cortex. Behav Brain Res. 2007 Jan 10;176(1):75-93. Epub 2006 Nov 7. PubMed PMID: 17084912.

171. Machado CJ, Bachevalier J. The effects of selective amygdala, orbital frontal cortex or hippocampal formation lesions on reward assessment in nonhuman primates. Eur J Neurosci. 2007 May;25(9):2885-904. PubMed PMID: 17561849.

172. Machado CJ, Bachevalier J. Measuring reward assessment in a semi-naturalistic context: the effects of selective amygdala, orbital frontal or hippocampal lesions.

Neuroscience. 2007 Sep 7;148(3):599-611. Epub 2007 Aug 10. PubMed PMID: 17693034; PubMed Central PMCID: PMC2064940.

173. Shamy JL, Buckmaster CA, Amaral DG, Calhoun ME, Rapp PR. Reactive plasticity in the dentate gyrus following bilateral entorhinal cortex lesions in cynomolgus monkeys. J Comp Neurol. 2007 May 10;502(2):192-201. PubMed PMID: 17348008.

174. Bachevalier J, Nemanic S. Memory for spatial location and object-place associations are differently processed by the hippocampal formation, parahippocampal areas TH/TF and perirhinal cortex. Hippocampus. 2008;18(1):64-80. PubMed PMID: 17924520.

175. Chudasama Y, Wright KS, Murray EA. Hippocampal lesions in rhesus monkeys disrupt emotional responses but not reinforcer devaluation effects. Biol Psychiatry. 2008 Jun 1;63(11):1084-91. doi: 10.1016/j.biopsych.2007.11.012. Epub 2008 Jan 11. PubMed PMID: 18191111.

176. Machado CJ, Bachevalier J. Behavioral and hormonal reactivity to threat: effects of selective amygdala, hippocampal or orbital frontal lesions in monkeys. Psychoneuroendocrinology. 2008 Aug;33(7):926-41. doi: 10.1016/j.psyneuen.2008.04.012. Epub 2008 Jul 22. PubMed PMID: 18650022; PubMed Central PMCID: PMC2564854.

177. Bauman MD, Toscano JE, Babineau BA, Mason WA, Amaral DG. Emergence of stereotypies in juvenile monkeys (Macaca mulatta) with neonatal amygdala or hippocampus lesions. Behav Neurosci. 2008 Oct;122(5):1005-15. doi: 10.1037/a0012600. PubMed PMID: 18823158; PubMed Central PMCID: PMC2884986.

178. Pascalis O, Hunkin NM, Bachevalier J, Mayes AR. Change in background context disrupts performance on visual paired comparison following hippocampal damage. Neuropsychologia. 2009 Aug;47(10):2107-13. doi: 10.1016/j.neuropsychologia.2009.04.001. Epub 2009 Apr 9. PubMed PMID: 19467361.

179. Toscano JE, Bauman MD, Mason WA, Amaral DG. Interest in infants by female rhesus monkeys with neonatal lesions of the amygdala or hippocampus. Neuroscience. 2009 Sep 15;162(4):881-91. doi: 10.1016/j.neuroscience.2009.05.056. Epub 2009 May 29. PubMed PMID: 19482067; PubMed Central PMCID: PMC2836226.

180. Chudasama Y, Izquierdo A, Murray EA. Distinct contributions of the amygdala and hippocampus to fear expression. Eur J Neurosci. 2009 Dec;30(12):2327-37. doi: 10.1111/j.1460-9568.2009.07012.x. Epub 2009 Dec 10. PubMed PMID: 20092575; PubMed Central PMCID: PMC2852103.

181. Jutras MJ, Buffalo EA. Recognition memory signals in the macaque hippocampus. Proc Natl Acad Sci U S A. 2010 Jan 5;107(1):401-6. doi: 10.1073/pnas.0908378107. Epub 2009 Dec 14. PubMed PMID: 20018683; PubMed Central PMCID: PMC2806723.

182. Muñoz M, Mishkin M, Saunders RC. Resection of the medial temporal lobe disconnects the rostral superior temporal gyrus from some of its projection targets in the frontal lobe and thalamus. Cereb Cortex. 2009 Sep;19(9):2114-30. doi: 10.1093/cercor/bhn236. Epub 2009 Jan 15. PubMed PMID: 19150921; PubMed Central PMCID: PMC2722427.

2010s

183. Bliss-Moreau E, Toscano JE, Bauman MD, Mason WA, Amaral DG. Neonatal amygdala or hippocampus lesions influence responsiveness to objects. Dev Psychobiol. 2010 Jul;52(5):487-503. doi: 10.1002/dev.20451. PubMed PMID: 20583145; PubMed Central PMCID: PMC4577025.

184. Zeamer A, Meunier M, Bachevalier J. Stimulus similarity and encoding time influence incidental recognition memory in adult monkeys with selective hippocampal lesions. Learn Mem. 2011 Feb 25;18(3):170-80. doi: 10.1101/lm.2076811. Print 2011. PubMed PMID: 21357439; PubMed Central PMCID: PMC3056513.

185. Heuer E, Bachevalier J. Effects of selective neonatal hippocampal lesions on tests of object and spatial recognition memory in monkeys. Behav Neurosci. 2011 Apr;125(2):137-49. doi: 10.1037/a0022539. PubMed PMID: 21341885; PubMed Central PMCID: PMC3072249.

186. Chau VL, Murphy EF, Rosenbaum RS, Ryan JD, Hoffman KL. A Flicker Change Detection Task Reveals Object-in-Scene Memory Across Species. Front Behav Neurosci. 2011 Sep 20;5:58. doi: 10.3389/fnbeh.2011.00058. eCollection 2011. PubMed PMID: 21960963; PubMed Central PMCID: PMC3176411.

187. Heuer E, Bachevalier J. Neonatal hippocampal lesions in rhesus macaques alter the monitoring, but not maintenance, of information in working memory. Behav Neurosci. 2011 Dec;125(6):859-70. doi: 10.1037/a0025541. Epub 2011 Sep 19. PubMed PMID: 21928873; PubMed Central PMCID: PMC3226899.

188. Croxson PL, Browning PG, Gaffan D, Baxter MG. Acetylcholine facilitates recovery of episodic memory after brain damage. J Neurosci. 2012 Oct 3;32(40):13787-95. doi: 10.1523/JNEUROSCI.2947-12.2012. PubMed PMID: 23035090; PubMed Central PMCID: PMC3475489.

189. Glavis-Bloom C, Alvarado MC, Bachevalier J. Neonatal hippocampal damage impairs specific food/place associations in adult macaques. Behav Neurosci. 2013 Feb;127(1):9-22. doi: 10.1037/a0031498. PubMed PMID: 23398438; PubMed Central PMCID: PMC3736558.

190. Templer VL, Hampton RR. Cognitive mechanisms of memory for order in rhesus monkeys (Macaca mulatta). Hippocampus. 2013 Mar;23(3):193-201. doi: 10.1002/hipo.22082. Epub 2012 Nov 29. PubMed PMID: 23197396; PubMed Central PMCID: PMC3757570.

191. Zeamer A, Bachevalier J. Long-term effects of neonatal hippocampal lesions on novelty preference in monkeys. Hippocampus. 2013 Sep;23(9):745-50. doi: 10.1002/hipo.22139. Epub 2013 Jun 6. PubMed PMID: 23640834; PubMed Central PMCID: PMC3775855.

192. Meng Y, Payne C, Li L, Hu X, Zhang X, Bachevalier J. Alterations of hippocampal projections in adult macaques with neonatal hippocampal lesions: A Diffusion Tensor Imaging study. Neuroimage. 2014 Nov 15;102 Pt 2:828-37. doi: 10.1016/j.neuroimage.2014.08.059. Epub 2014 Sep 7. PubMed PMID: 25204865; PubMed Central PMCID: PMC4252575.

193. Kwok SC, Mitchell AS, Buckley MJ. Adaptability to changes in temporal structure is fornix-dependent. Learn Mem. 2015 Jul 15;22(8):354-9. doi: 10.1101/lm.038851.115. Print 2015 Aug. PubMed PMID: 26179228; PubMed Central PMCID: PMC4509921.

194. Chareyron LJ, Amaral DG, Lavenex P. Selective lesion of the hippocampus increases the differentiation of immature neurons in the monkey amygdala. Proc Natl Acad Sci U S A. 2016 Dec 13;113(50):14420-14425. Epub 2016 Nov 28. PubMed PMID: 27911768; PubMed Central PMCID: PMC5167145.

195. Bliss-Moreau E, Moadab G, Santistevan A, Amaral DG. The effects of neonatal amygdala or hippocampus lesions on adult social behavior. Behav Brain Res. 2017 Mar 30;322(Pt A):123-137. doi: 10.1016/j.bbr.2016.11.052. Epub 2016 Dec 22. PubMed PMID: 28017854; PubMed Central PMCID: PMC5423538.

196. Heimer-McGinn VR, Poeta DL, Aghi K, Udawatta M, Burwell RD. Disconnection of the Perirhinal and Postrhinal Cortices Impairs Recognition of Objects in Context But Not Contextual Fear Conditioning. J Neurosci. 2017 May 3;37(18):4819-4829. doi: 10.1523/JNEUROSCI.0254-17.2017. Epub 2017 Apr 14. PubMed PMID: 28411272; PubMed Central PMCID: PMC5426571.

197. Vil-Balla, Mas-Herrero E, Ripollos P, Sim M, Mir J, Cucurell D, Lopez-Barroso D, Juncadella M, Marco-Pallaros J, Falip M, Rodrguez-Fornells A. Unraveling the Role of the Hippocampus in Reversal Learning. J Neurosci. 2017 Jul 12;37(28):6686-6697. doi: 10.1523/JNEUROSCI.3212-16.2017. Epub 2017 Jun 7. PubMed PMID: 28592695.

198. Rueckemann JW, Buffalo EA. Spatial Responses, Immediate Experience, and Memory in the Monkey Hippocampus. Curr Opin Behav Sci. 2017 Oct;17:155-160. doi: 10.1016/j.cobeha.2017.08.008. Epub 2017 Sep 5. PubMed PMID: 29255777; PubMed Central PMCID: PMC5731786.

199. Chareyron LJ, Banta Lavenex P, Amaral DG, Lavenex P. Functional organization of the medial temporal lobe memory system following neonatal hippocampal lesion in rhesus monkeys. Brain Struct Funct. 2017 Dec;222(9):3899-3914. doi: 10.1007/s00429-017-1441-z. Epub 2017 May 9. PubMed PMID: 28488186.

200. Raper J, Wilson M, Sanchez M, Payne C, Bachevalier J. Increased anxiety-like behaviors, but blunted cortisol stress response after neonatal hippocampal lesions in monkeys. Psychoneuroendocrinology. 2017 Feb;76:57-66. doi: 10.1016/j.psyneuen.2016.11.018. PubMed PMID: 27888771; PubMed Central PMCID: PMC5272817.

201. Moadab G, Bliss-Moreau E, Bauman MD, Amaral DG. Early amygdala or hippocampus damage influences adolescent female social behavior during group formation. Behav Neurosci. 2017 Feb;131(1):68-82. doi: 10.1037/bne0000181. Epub 2017 Jan 5. PubMed PMID: 28054806; PubMed Central PMCID: PMC5269439.

APPENDIX II: COMPLETE BIBLIOGRAPHY OF HIPPOCAMPAL NEUROPHYSIOLOGY IN BEHAVING NON-HUMAN PRIMATES

The following pages contain the citation and key findings from every study of non-human primate hippocampal single neuron electrophysiology published to date. Note, preliminary reports, conference proceedings, review articles, book chapters, and studies in anaesthetized monkeys are excluded.

Reference	Behaviour	Hippocampal neural responses	Additional notes
Yokota *et al*. 1967, *Science*	Intracellular hippocampal pyramidal neuron recording during olfactory bulb or septal stimulation	Olfactory bulb: elicited EPSPs 24% of neurons; no action potentials. Septum: elicited EPSPs and action potentials.	Follow-up study to Gergen & Maclean 1964, which reported effects on local field potentials. EPSP latency following olfactory bulb stimulation was longer than entorhinal cortex stimulation, suggesting olfactory information transmitted via entorhinal cortex.
Fuster & Uyeda 1971, *Electroecephalog Clin Neurophys*	Visual discrimination task	61% task responsive; 25% stimulus selective	More units were task-responsive in the hippocampus than amygdala; more neurons were stimulus-selective in the amygdala.
Watanabe & Niki 1985, *Brain Res*	Spatial DR task	14.7% task-responsive; 6.3% of these neurons spatially-selective (0.009% of all neurons).	1848 neurons were recorded total. It cannot be determined whether spatially responsive units fired in relation to the remembered location, or the prepared motor response.
Cahusac et al. 1989, Behav Brain Res	1) Spatial DR task 2) Object-location DMS task	1) 5.7% location selective 2) 3.8% location selective	Neurons recorded in hippocampus and hippocampal gyrus. Neural responses were analyzed during object (image) presentation on a video monitor. ANOVA for novel and familiar stimuli in each position; further inference was derived using posthoc tests.
Rolls et al. 1989, J Neurosci	1) Spatial DR task 2) Serial object-location DR task	1) 10.2% location selective 2) 2.4% location selective;	Neurons and statistics as in Cahusac *et al.* 1989. 4 of 8 neurons that were location selective in 2) also responded differentially between novel and repeated objects, suggesting that spatial information is not the sole determinant of firing rate for this subset of neurons. No neurons were reported as object-in-location selective.
Miyashita et al. 1989, J Neurophysiol	Stimulus-response task	14% trial type selective	Neurons recorded as in Cahusac *et al.* 1989. Selectivity was assessed during stimulus presentation on "respond" versus "hold" trials during visual stimulus presentation using a Student's *t* test.

Tamura et al. 1990, Neurosci Lett	Passive auditory or visual stimulus presentation	10% initially audio and/or visual stimulus place selective; estimated 3.6% egocentric; estimated 2.4% allocentric; estimated 4.2% lose selectivity after rotation.	Visual stimuli included an apple, raisin, spider model, stick, human actions, and more. Auditory stimuli included harmonic rich or pure tines, a voice, a monkey cry, a step, clap, crash, and more. Statistics used were not reported. These results are mostly recapitulated in Ono *et al*. 1991, *Hippocampus*, as well as Tamura *et al*. 1992, *Hippocampus*.
Wilson et al. 1990, Behav Brain Res	Conditional object DMS task	38-48% active at behavioural response; 33.5% also responsive to visual stimuli; 17% left- vs right-selective	Monkeys were trained to look at two sequential stimuli, with a match requiring a right panel press (DMS), and a nonmatch requiring a left panel press (DMNS). Some stimuli were highly familiar, and others were not. Subsets of neurons were direction-selective around the time of the behavioural response, as well as during stimulus presentation.
Feigenbaum & Rolls 1991, *Psychobiol*	Spatial DR task, moving the monkey and monitor around the lab	7% egocentric spatial; 61% allocentric spatial;	The majority of "allocentric" cells were "frame-of-reference allocentric"; that is, their spatial response fields were defined by the local frame provided by the monitor screen. Fewer were "absolute allocentric" cells, with fields defined by the monitor position in the room, independent of position relative to the monkey's body axis or to position on the monitor screen face.
Cahusac et al. 1991, Neurosci Lett	Stimulus-response task	Only examined potentiation in stimulus selective neurons	Same task as Miyashita *et al*. 1989, *J Neurophysiol*. Local L-glutamate application during stimulus presentation caused object-specific potentiation of responses in 21% of neurons.
Vidyasagar *et al.* 1991, *Brain Res*	Object DMS	28.5% task responsive; None responsive during delay period or inter-trial interval.	Highly familiar objects were used; thus, this is not like the DMS task deemed highly sensitive to hippocampal lesion by Mishkin and Gaffan in the 1970s and 1980s.

Tamura et al. 1991, Brain Res Bull	Stimulus-response	18.4% stimulus-presentation responsive; 9.8% object-selective	Monkeys sat in front of a viewing window and operant response bar. Depending on the object, response would result in a food reward, juice reward, or avoidance of electric shock. These results are mostly repeated in Tamura *et al*. 1992, *Hippocampus*, with some units from parahippocampal cortices added.
Riches *et al*. 1991, *J Neurosci*	Conditional object DMS task	45.7-59.8% cue or test stimulus selective; None selective for stimulus novelty/familiarity	Same task and dataset as Wilson *et al*. 1990. Few neurons were tested with novel versus familiar stimuli by Rolls *et al*. 1989; however, half of those were differentially responsive.
Ono et al. 1993, J Neurophysiol	Stimulus-response joystick movement, resulting in robotic cab movement around lab	46% task-responsive; 33% place selective	Part of this dataset was published in Ono *et al*. 1991, *Neurosci Lett* and again in Ono *et al*. 1991, *Hippocampus*. During the inter-trial interval, the movable cab could be rotated in place. Statistical methods: the explorable area was divided into pixels, and mean firing rate in each pixel was calculated. Any pixel with a firing rate two times that of the grand mean across pixels seeded a place field; fields extended to pixels with firing rates >1.5 times the grand mean. Effects of confounding factors were not examined.
Cahusac *et al*. 1993, *Hippocampus*	Stimulus-response learning	For task responsive neurons: sustained stimulus-differential responses emerged in 21.8% of experiments; transient differential responses in 45% of experiments.	For many, but not all neurons, the same task was used in Miyashita *et al*. 1989, *J Neurophysiol*. However, authors now examined changes in neuronal activity during learning stimulus-response mappings for new objects.
Rolls et al. 1993, Exp Brain Res	Serial object recognition	2.3% novelty versus familiarity selective	These 15 neurons were not reward selective, as shown using a visual discrimination task.

O'Mara *et al*. 1994, *J Neurosci*	Passive movement	9.8% responsive to some factor, including axial rotation, linear translation; 0.007% movement and place or rotation selective	Movement of monkeys seated in a chair and chamber within a laboratory. Experimenters tested a number of conditions in subsets of cells. The largest set of neurons seemed selective to whole-body movement. Tests with occluded visual fields suggested view was important for many neurons. Eye position and gaze position were not recorded.
Rolls & O'Mara 1995, *Hippocampus*	Passive rotation	5.6% view selective	Authors report the effect of systematic variation of 1) place and 2) view rotation within the experiments described by O'Mara *et al*. 1994. Some view selective neurons were sensitive to place in the environment, while others were not.
Eifuku *et al*. 1995, *J Neurosci*	Spatially conditional stimulus-response	27% task responsive; 5% trial feature selective	Of the task-responsive neurons 56% were also responsive during a stimulus-response task, suggesting these neurons may respond to elements of the task that are not related to the conditional association itself.
Nishijo et al. 1997, Neurosci Lett	Passive movement	0-14% similarly place selective	Same task/dataset as Ono *et al*. 1993, *J Neurophysiol*, with passive movement. Of the 79 place selective neurons in Ono *et al*. 1993, 14 were tested for place selectivity during passive movement; per-pixel correlation of firing rates across movement conditions was not significant in any neurons; two neurons had similar place fields using other methods.
Rolls *et al*. 1997, *EJN*	Foraging in custom chair; active or passive movement	11% spatial view selective	First study in which monkeys could freely explore an environment while gaze position was tracked; 50% of view selective neurons were recorded in the hippocampus, 50% in the parahippocampal gyrus.
Robertson et al. 1998, J Neurophysiol	Foraging in custom chair; active or passive movement	Of spatial view cells: 8/12 responsive with view field obscured (CA1, not CA3); 11/15 responsive during locomotion (CA1, not CA3)	Same task/dataset as Rolls *et al*. 1997, *EJN*. All neurons with spatial view fields during locomotion maintained their spatial view fields. Note, sparsity and information content of neurons and the ensemble were examined by Rolls, Treves, Robertson, Georges-Francois & Panzeri 1998. *J Neurophysiol*.

Colombo et al 1998, J Neurophysiol	Spatial DMS and non-spatial DMS task (interleaved)	43% delay responsive; 16% spatial delay responsive only; 3% face-cue delay responsive only; 2% object-cue delay responsive only	Paired t-test on firing rate during the baseline period (inter-trial interval) and the delay period for every neuron, for every trial type. An important note is that of 33 neurons a significant result, 29 are inhibitory delay neurons, and 12 are excitatory delay neurons.
Xiang & Brown 1999, *EJN*	Conditional associative learning or stimulus-response	13% cue selective	Authors report this as a conditional associative learning task; however, alternative cognitive strategies could be used by monkeys to solve the task.
Georges-François *et al*. 1999, *Cereb Cortex*	Foraging in custom chair; active or passive movement		Same task/dataset as Rolls *et al*. 1997 EJN, Robertson *et al.* 1998, *J Neurophysiol* and Rolls *et al*. 1998, *J Neurophysiol* 1998. Authors specifically test null hypothesis that spatial view cells are not allocentric using an ANOVA, and by quantifying spatial information content using an allocentric reference frame.
Matsumura *et al* 1999, *J Neurosci*	1) Wayfinding in a motorized cab; 2) Analogous pointer task with joystick and video screen	43% place selective in at least one task; 4% of neurons with partially overlapping place fields 1) 39% place selective 2) 26% place selective	Neurons were recorded in the hippocampus and parahippocampal gyrus. Place fields were defined as in Ono *et al*. 1993. Note, a variant of each task was also included, with either target location and/or virtual pointer location not visible during movement. Authors do not monitor gaze, quantify the effect of direction, or cite the view-specificity observed by Rolls *et al*. Note, the cross-task similarity of firing rate maps was examined again by Hori *et al*. 2003, *Hippocampus*.
Hori et al. 2003, Hippocampus	1) Wayfinding in a motorized cab; 2) Analogous pointer task with joystick and video screen		Same task/dataset as Matsumura *et al*. 1999, *J Neurosci*. Authors use multidimensional scaling to examine the correlation between spatial firing rate maps across tasks; previously, a correlation was used.

Wirth *et al*. 2003, *Science*	Scene-location associative learning	61% scene responsive; 48% delay period responsive; 17% correlated with learning	Of the 17% of neurons whose activity modulation correlated with learning, both negative and positive correlations were observed.
Yanike *et al*. 2004, *Neuron*	Scene-location associative learning	67% task responsive; 51% scene responsive;	Same neurons and task as in Wirth *et al*. 2003. Most scene-location associations were novel every day, except for four well-learned scene-location associations that were repeated every day.
Ludvig *et al*. 2004, *Brain Res*	In-cage foraging	32% place specific	Squirrel monkeys moved around a cage, foraging in food ports for reward. Pixels with firing rates 5 times the neuron's mean firing rate created place fields.
Hampson *et al*. 2004, *PNAS*	Multi-image DMS	10.5% Trial start; 20.6% Sample phase; 14.5% Match phase; 10.9% Delay interval; 19.8% Image category;	Image category selective neurons had lower firing rates when: 1) the test phase on incorrect versus correct trials, and 2) morphed stimuli with some, but not all, features of the preferred sample stimulus were used.
Hori et al. 2005, Hippocampus	Virtual navigation	31% place selective	Place fields were defined as in Ono *et al*. 1993. Extramaze cues were moved in the virtual environment. 16.5% of neurons had place fields in only one configuration; 4.7% of neurons had place fields in multiple configurations, with a correlation coefficient <0.3 across configurations.
Rolls et al. 2005, J Neurosci	Scene-location association learning	22% reward magnitude selective; 7.7% scene selective;	Reward magnitudes at each location were switched for some neurons; 60% of neurons were selective for the new location; 20% were selective for the same location; 20% stopped firing differentially across locations.

Rolls et al. 2005, J Neurophysiol	Object-location association learning	10% object selective; 12% location selective; 10% place and location selective.	Monkeys were seated in front of two monitors, and each object was rewarded when presented on one monitor and punished when presented on the other. Some location-selective neurons were tested after the monkey was moved; 66% showed allocentric selectivity, whereas 21% showed egocentric selectivity.
Wirth *et al*. 2009, *Neuron*	Object-location association learning	77% task responsive; 50% outcome selective during inter-trial interval.	All comparisons were done using t-tests and ANOVAs. 18% of neurons increased firing rate after correct trials; 23% increased firing rate after incorrect trials; 3% decreased firing rate after correct trials; 4% decreased firing rate after error trials; 2% were different than baseline after both correct and error trials. "Correct-up" neurons changed stimulus selectivity as a function of learning.
Jutras & Buffalo 2010, *PNAS*	Free scene viewing	24% novel vs. familiar selective	Exploiting monkeys' natural tendencies, authors inferred memory/recognition from time spent viewing scenes on novel versus repeated presentations.
Hori et al 2011, Front Behav Neurosci	1) Wayfinding in a motorized cab; 2) Analogous pointer task with joystick and video screen	44% of simultaneously recorded neuron pairs showed significant cross-correlation in activity patterns	Same task/dataset as Matsumura *et al*. 1999, *J Neurosci*.
Thomé et al. 2012, Hippocampus	Free scene viewing	4% novel vs. familiar selective	Neurons in area TF changed their activity based on scene familiarity, whereas neurons in CA3 or the perirhinal cortex did not.
Hampson et al. 2013, J Neural Eng	Spatial DMS and non-spatial DMS task (interleaved)	Statistics not suitable	Statistics appear to be done only on population firing rates, rather than statistical reports of firing rate for each neuron
Furuya et al. 2014, Hippocampus	1) Wayfinding 2) Virtual Pointer task	1) 73% place-selective 2) 26% place-selective	Place fields were defined as any pixels greater than 2 times a biased estimate of mean firing rate for that neuron.

Brincat & Miller 2015, *Nat Neurosci*	Object-object associative learning	Hippocampal neurons selective for trial	The activity of hippocampal neurons after the trial outcome was used to predict outcome with an accuracy of 89%
Deadwyler *et al*. 2015, *Brain Res*	Spatial DMS and non-spatial DMS task (interleaved)	Statistics not suitable	Same task as Hampson *et al*. 2013, *J Neural Eng*.
Thomé et al. 2016, Mol Psychiatry	Object DMS task	Baseline firing rates in CA3 higher in older than younger animals.	Difference in baseline firing rate was negatively correlated with interneuron density and task performance.
Sliwa et al. 2016, *Cereb Cortex*	Passive viewing or listening	20% face selective; 15% voice selective; 6% sound selective;	Authors found similar neuronal and population-level coding of identity in the hippocampus and TE for both vocal and facial identity. Individual identity in these two modalities was not particularly correlated, and faces were generally more informative than vocal stimuli.
Deadwyler *et al*. 2017, *Exp Neurol*	Spatial DMS and non-spatial DMS task (interleaved)	Statistics not suitable	Same task as Hampson *et al*. 2013, *J Neural Eng*.
Wirth *et al*. 2017, *PLoS Biol*	VR wayfinding; goal-directed navigation	36% allocentric place selective; 43% selective for conjunction of place and task-related factors	Proportions based on spatial information content. Of those that contain information about space and other task factors, 5% encoded more information about space than conjunctive coding

APPENDIX III: SURGICAL PROCEDURES

Many of the surgical techniques used for the completion of this thesis had not been done previously in our lab. Thus, considerable effort went into the development and refinement of techniques in order to optimize outcomes for animals, experimenters, and the experimental procedures. For posterity, a succinct description of the surgical protocols developed in during the completion of this thesis is included. These protocols and insights from these procedures led to continued development of a new complete cap system in our laboratory, designed to be less invasive with considerable health benefits to our non-human primate subjects. These caps can be modified for use across species. The complete cap system is detailed in (Blonde et al., 2018).

Instructions begin with the animal anaesthetized (the veterinary technician, does this). You should be in scrubs, a hair net, mask, face shield, shoe covers and gloves.

Pre-sterile appraisal and cleaning

1. Place the Brainsight computer and Polaris camera at their appropriate position in the room.
2. Clean the monkey's head using a chlorhexidine scrub and water, for 5-10 minutes.
   2.1. With clean hands, place the monkey's head on a sterile drape, so that it remains clean. Do not touch the monkey's body or any non-sterile surface and then touch the head.
   • Chlorhexidine scrub and water

3. Scrub in. Anything that is manipulated from this point on must be sterilized (autoclave or gas). Have a non-sterile assistant manipulate the monkey's head during steps 6-12, touching only the non-sterile base of the head, neck or mouth.

Sterile cleaning and head fixation

4. Cover the back and underside of the chair with a sterile drape, so sterile persons won't be contaminated. Use a fenestrated drape where the cylindrical rods will attach to the chair.
   • Sterile drapes

5. Use an iodine scrub to sterilize the monkey's head. Rest the head on a new drape.
   - Iodine scrub
   - Sterile drape
6. Install main cylindrical rods on the chair. Do not touch non-sterile surfaces.
   - Cylindrical rods
   - Large hex key
7. Prepare the C-clamp.
   7.1. Screw the wing nuts on to the 4-inch bone screws (4×).
   7.2. Assess which holes of the C-clamp the bone pins should go through to secure the monkey's head.
   7.3. Attach one star burst clamp to the middle of the C-clamp (this will attach to the cylindrical rods).
   7.4. If a the free-arm guide will be used, assess which position of the C-clamp this star burst clamp should take, and attach it securely to the C-clamp.
   7.5. Put sterile lubricant on gauze and dip the back of the bone pins in.
   This is done so the bone pin tip can rotate when screwing the pins to the skull rather than twist or tear tissue and muscle).
   7.6. Put the temporal bone pins into the appropriate positions on the C-clamp.
   7.7. If necessary, adjust the position of the cylindrical rods to accommodate the C-clamp and monkey's head while keeping a comfortable position.
   - 4× 4-inch bone screws
   - 4× wing nuts
   - C-clamp
   - Star burst clamp (2×)
   - Star burst clamp screw (2×)
   - Hex key for screw (2×)
   - Sterile lubricant
   - Sterile gauze
   - Bone pins (4×)
8. Insert the temporal bone pins.
   8.1. While the vet tech holds the monkey upright, make one small stab incision on each temporal side with scalpel.
   It is imperative that incisions reach the temporal bone, and penetrate muscle cleanly.

8.2. Tighten temporal screws until you reach the temporal bones through the incisions. Apply downward pressure on the C-clamp and ensure the screws do not slip on bone or muscle.

8.3. Using the torque wrench, carefully apply 2 lbs/in^2 pressure on bone screws (6-8 lbs/in^2 risks the temporal bone). Alternatively, tighten the screws manually.
NB: The C-clamp is not attached to the chair at this point.

- Scalpel (small)
- Torque wrench

9. Insert the occipital/transverse sinus bone pins.
   9.1. Put the occipital bone pins into the appropriate positions on the C-clamp.
   9.2. Make two perpendicular incisions under the transverse sinus where the two occipital bone screws will fall on the bone.
   9.3. Tighten the occipital screws below the transverse sinus, firmly fixing the head in the C-clamp. Tighten the left and right alternately, until both are secure.
10. Tighten all 4 wing nuts so the screws don't move during surgery. Make sure the monkey's head is held strongly by the C-clamp.
11. Attach the star burst clamp from step 7.3 (middle star bust clamp) to the cylindrical rods using the angled screw.
    11.1. If necessary, again adjust the position of the cylindrical rods to put the monkey's head in a proper orientation for the surgery.
    11.2. Have SN adjust the body position of the monkey to accommodate this new position.
    - Angled screw
12. Put a fenestrated sterile drape over the head; fix in place with towel hemostats.
    - Fenestrated drape
    - Curved towel hemostats
    - Sterile stapler

Chamber implant procedure

13. Assess chamber placement and make incisions.
    13.1. Double check the C-clamp and head stability.
    13.2. Use the reconstructed skull to assess chamber positioning.
    13.3. Prepare the incisions, and marking lines with a sterile marker.

13.4. When ready, cut through the skin using the scalpel, so that it may retract away. If suitable, use a tissue retractor to expose the chamber site.
NB: Julio instructs to avoid cutting through the muscle, as this will need to be sutured later. Cut only through the skin and immediately underlying layer, and use the tissue cauterizer to separate the skin and tissue away from the muscle.

• 3D printed skull

• Sterile marker

• Scalpel (large)

• Tissue retractor

• Cauterizer

14. Using a heavy bone scraper, clear all muscle and tissue from the bone. Clean the skull using gauze and saline to clean surface. Peroxide may stem bleeding.
    • Bone scraper (large and small)
    • Gauze
    • Saline
        • Peroxide
15. Remove the chamber lid, keeping track of all of the screws. Place the chamber on the intended site and trace its outline (outside, inside, and screw holes) with a sterile marker.
    • Chamber, lid and screws
        • Philips #000 screw driver
        • Sterile marker
16. Using the hand drill and a small bur, create small pilot holes where the three titanium skulls will secure the chamber to the skull.
        • Hand drill
        • Small bur
17. Remove the chamber, and open the craniotomy using the hand drill, using the lines drawn as a guide.
18. Secure the chamber.
    18.1. When the craniotomy is made, place the chamber back over the site and gently screw the three titanium screws in to the bone.
    Very gently secure all three at first.

18.2. With the screws secure to the bone, it should be possible to lift the chamber gently, creating a gap between the skull and the bottom of the chamber.

NB: 18.3-18.6 must be finished within 30-90 seconds.

18.3. With the lid lifted, apply Denmat Geristore to the skull, over the line traced at the outside border of the chamber bottom.

18.4. *QUICKLY:* Press down chamber on to the Denmat and skull.

18.5. *QUICKLY:* With this secured, use the hand-drills to secure the screws.

18.6. *QUICKLY:* Use the wooden lozenges to remove any excess Denmat.

18.7. Use Denmat Geristore to close any remaining gaps between the chamber and the skull, on the inside, outside and surrounding the legs.

- 3 titanium screws (may have extra ready in case screws are dropped)
- Denmat Geristore
- Hand hex head screw drivers

19. Apply Qwik-Sil to the inside of the chamber, creating a hermetic seal between the cerebrospinal fluid and the environment.

19.1. Take a photograph of the inside of the chamber immediately before and after Qwik-Sil application.

20. When chamber is secured, use acrylic or bone cement to cover the screw heads and fill any gaps between the head post and skull, or screws and head post.

- Acrylic
- Petrie dishes
- Spatula

21. Once the acrylic is dried and chamber stability is ensured, the wound may be closed. Pull the skin back over the head post to join the two sides of the wound. Palpate the top of the head post, and make small, clean incision through all layers of the scalp so that the head post will protrude from this hole (ensuring the smallest possible open wound). Use mosquito hemostats to widen the initial incision, so that the skin tightly surrounds the head post (see photo). Clean the top of the head post of any blood, and attach the black head post cover.

- Mosquito hemostat

22. Suture the incision using horizontal or vertical (where necessary) mattress sutures spaced at least 5 mm apart (or use surgical staples). Clean wounds gently if desired.

- Sterile suture or stapler

23. Loosen wing nuts on the bone screws, and begin unscrewing to remove the head from the C-clamp. Have an assistant support the monkey, and as soon as possible, rest the monkey's head on a sterile surface such as the fenestrated drape. If necessary, make a simple interrupted suture (or staple) over the bone pin incisions (more likely necessary for temporal incisions than occipital ones). If any time remains before the vet tech takes over, try to clean any iodine or blood from the animal's skin.
    *This step must be done very quickly. As soon as one of the bone screws is undone, intracranial pressure drops, resulting in a rush of blood to the brain. As a result of this increased blood flow, the animal may rapidly become conscious.