Chapter title:

Studies of hippocampal function in non-human primates

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KEYWORDS

Macaca mulatta, monkey, primate, hippocampus, lesion, electrophysiology, behaviour, memory, spatial navigation, cognitive map, single neuron, neuropsychology, computational modelling

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 have been difficult to simultaneously observe and disentangle in lesion and electrophysiology studies. Together, the work reviewed in this chapter shows that some, but not all predictions of spatial and mnemonic theories of hippocampal function are corroborated in monkeys performing tasks that allow for precise measurement and parameterization of behaviour during electrophysiological experiments. The points of divergence from established dogmas may have important implications for neuropsychological and computational theories of hippocampal function across species.

KEY POINTS/OBJECTIVES

- Historically, the function of the hippocampus has been widely debated, with prominent theories including olfactory function, emotional regulation, memory storage, and spatial navigation
- Lesion and electrophysiological studies in non-human primates have been conducted to test tenets of these various theories, over a period of time spanning from the 19th century to the present day
- This chapter begins by providing a chronological history of studies of hippocampal function in non-human primates
- We attempt to bridge this body of work by suggesting that hippocampal circuits have evolved to compress experiences into memories, thereby serving a variety of neuropsychological functions

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

INTRODUCTION

"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).*

The hippocampus is the phylogenetically oldest area of the mammalian 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 it has not markedly diverged across species for millions of years of evolution. 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 contemporary understanding of the hippocampus is that this region receives highly processed information from all sensory modalities and this information is processed to subserve two cognitive functions: memory and spatial navigation (Schiller et al., 2015). One compelling theory suggests the primacy of spatial information in the mammalian hippocampus; furthermore, 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 from rodents completing tasks that require spatial navigation (see, e.g. Moser et al., 2017). The spatial navigation theory is so influential that in some cases, the identification of non-mammalian homologues of the hippocampus has been based on 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 a 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 both the spatial and non-spatial theories have branded each function the evolutionary *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, cross-species comparisons of activity amongst hippocampal neurons is complicated by evolutionarily divergent sensory systems, a corresponding reorganization of sensory inputs to the hippocampus, and diverse behavioural repertoires (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 and contributed to an increasing rate of publication in this field (Figure 1). Innovations in virtual reality platforms and wireless electrophysiology have allowed for the development of new paradigms to dissociate spatial and non-spatial response profiles in single neurons. In this chapter, we attempt to trace the arc of hippocampal research involving non-human primates closely, in hopes that this facilitates healthy scepticism towards the established dogmas of hippocampal function across species.

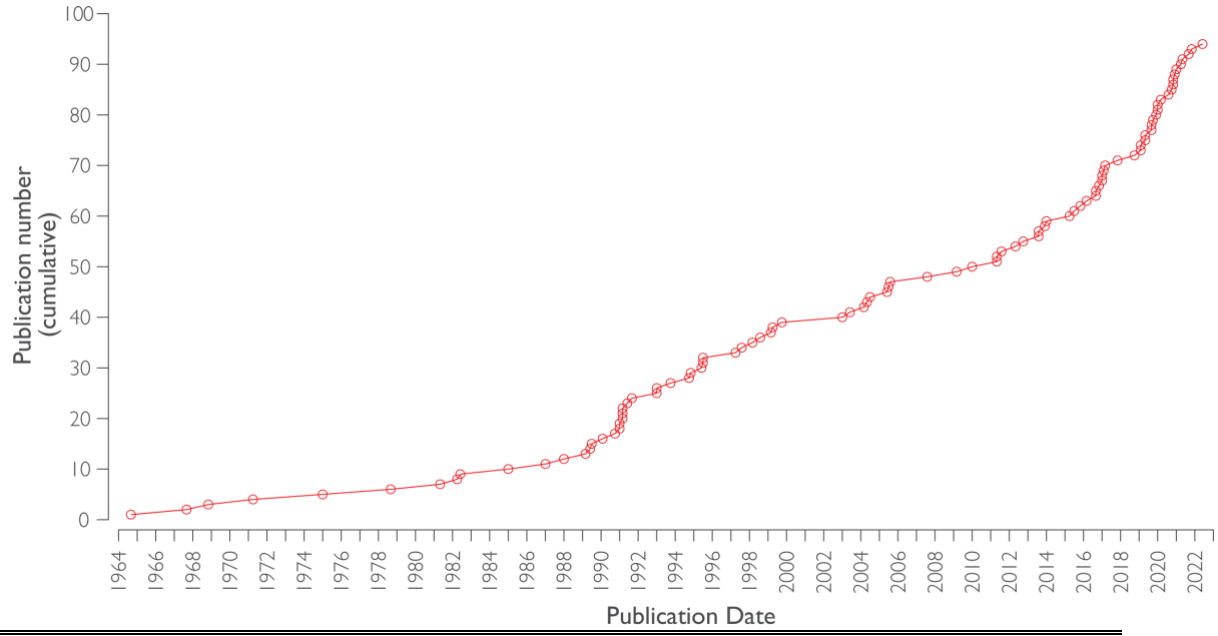

Figure 1. Cumulative number of non-human primate electrophysiology research articles.

As of August 2022, 94 primary research articles with electrophysiological recordings from the hippocampus of non-human primates had been published.

A CHRONOLOGY OF HIPPOCAMPAL RESEARCH IN NON-HUMAN PRIMATES

HIPPOCAMPAL RESEARCH PRIOR TO THE 1950S

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 colouration 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 psychological 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 during a public exhibition, and in print in 1888 (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 of 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 Ferrier's opinion. It was proposed that any deficits may be due not only to local disturbances of the cortex, but disturbances to the vasculature 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 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). Following this, little enters the public record for some time, presumably owing to effects of the global war.

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" (Papez, 1937). 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 with bilateral temporal lobectomy lacked anger or fear responses and investigated all objects -- animate and inanimate -- by placing them in their mouth (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 referenced 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

excision, 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 non-human primates in the following decades.

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

Summary

Prior to the mid-20th century, studies of the hippocampus not tightly focussed in terms of methodology or interpretation. 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, including anatomical studies of nonhuman primates. The prevailing view during this time was that the hippocampus was largely an extension of the olfactory system ("rhinencephalon"), and occasionally implicated in other primary sensory functions. 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. In the period of time between two global wars, further study of hippocampal connectivity within the limbic lobe suggested its role in emotional regulation, rather than specific forms of sensory or memory processing. Stimulation of temporal cortex in human patients suggested that the hippocampus may be part of "interpretive cortex", functioning to place incoming sensory inputs into environmental context, and store sensory representations as memories.

The 1950s

Lesion studies in the 1950s

Entering the 1950s, our understanding of cortex was very different than the current view. 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 non-human primates. Many investigators interested in studying the cognitive effects of localized lesions to many brain regions in non-human primates were critical of the principals 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 somaesthetic discrimination tasks, alternation tasks, and delayed reaction tasks. If tasks were

only administered after cortical lesion, experimenters claimed that animals' learning faculties were being assessed. Sometimes tasks were learned prior to lesion procedures, and the task performance was re-tested after lesions; 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. These types of studies became the dominant paradigm for experimental research in non-human primates.

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 named Mortimer Mishkin was sent to conduct experiments for his thesis work on localization of function with Pribram at Yale: this marked the start of an 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 2**; (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 3**; Mishkin, 1954).

ELECTROPHYSIOLOGICAL AND CLINICAL STUDIES IN THE 1950S

The first electrophysiological recordings from the hippocampus of 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, 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 animals in pursuit of a model of HM's deficits (Scoville and Correll, 1973).

SUMMARY

Two unrelated phenomena drove the direction of nonhuman primate hippocampal research in the 1950s. The description of anterograde amnesia in human patients with hippocampal damage incentivized researchers to create an animal model of these memory deficits. Furthermore, nonhuman primate researchers adopted the use of the Wisconsin General Testing Apparatus for neuropsychological testing. Using this experimental paradigm, a variety of studies were done to try to characterize neuropsychological deficits in monkeys

with a variety of temporal lobe lesions. However, little consensus regading the function of the hippocampus would be found across these studies through the 1950s and the ensuing decades. This decade also marked the first electrophysiological recordings from nonhuman primate hippocampus.

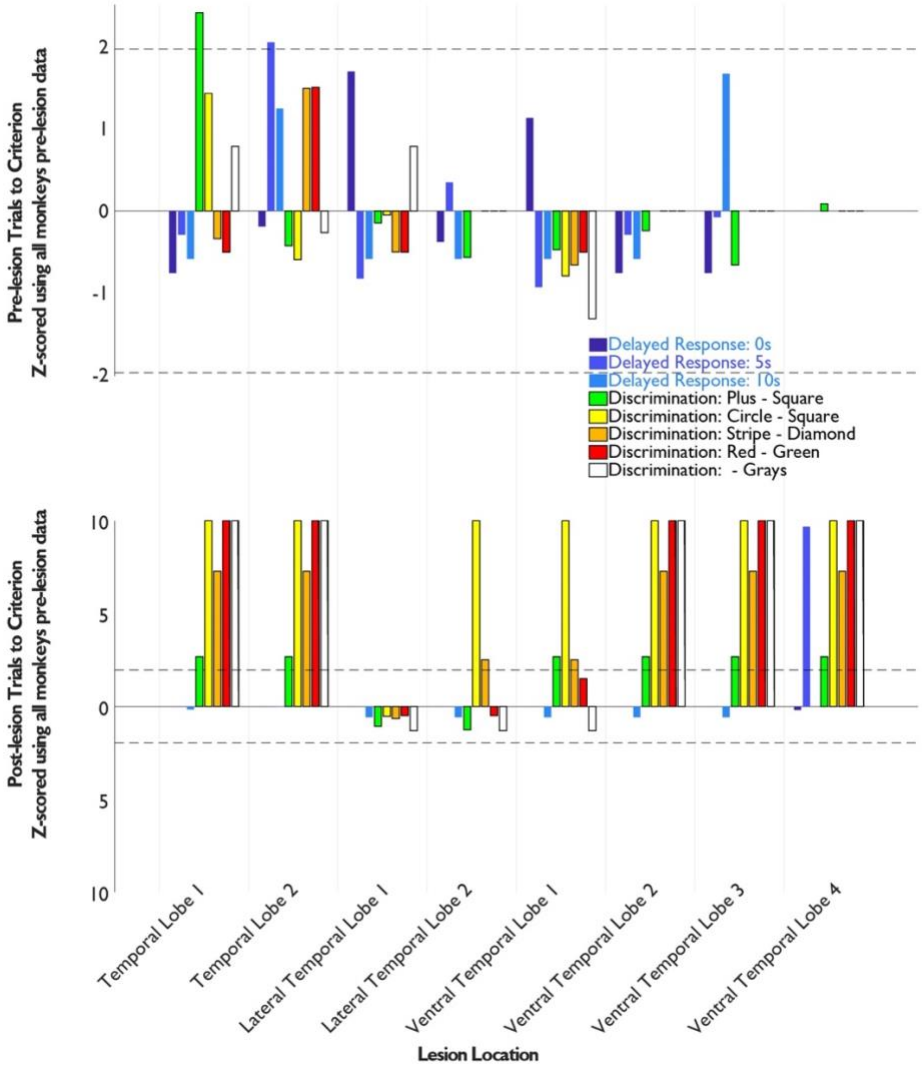

Figure 2. Results from Mishkin & Pribram (1954).

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.

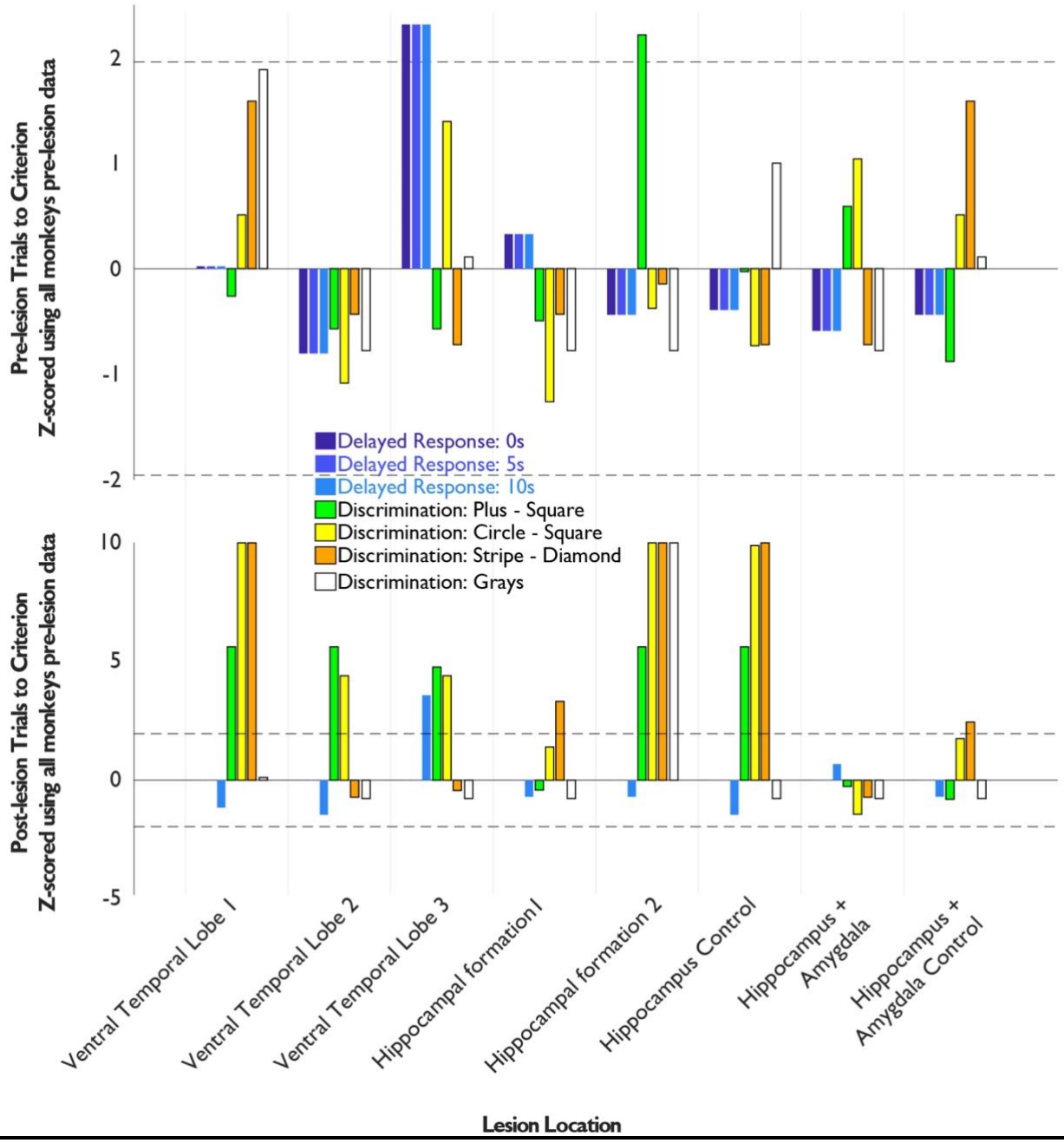

Figure 1. Results from Mishkin (1954).

Experimental lesion data from 8 monkeys extracted from (Mishkin, 1954) and shown graphically. Conventions as in Figure 2. Though not consistent, some temporal lobe ablations affect performance on visual discrimination tasks, but not delayed response.

THE 1960S

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 our 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 tasks (DMS; often used interchangeably with delayed response) and delayed-non-match-to-sample tasks (DNMS). Delayed response (DR) and delayed alternation tasks (DA) are like DMS and DNMS tasks, respectively, though the cue and test stimuli might not be identical 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 the 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 association tasks. The effects of hippocampal lesions conducted in non-human primates from this this point forward could be used to fill a volume unto itself. A notable subset of this literature is discussed in detail here.

The 1960s started with a highly influential attempt to replicate HM's deficits including experimental brain lesions in monkeys at McGill University (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 analysed; since lesion locations and behavioural tests across monkeys were not standardized, these results are difficult to interpret (see **Figure 4** 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; 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 5**). 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.

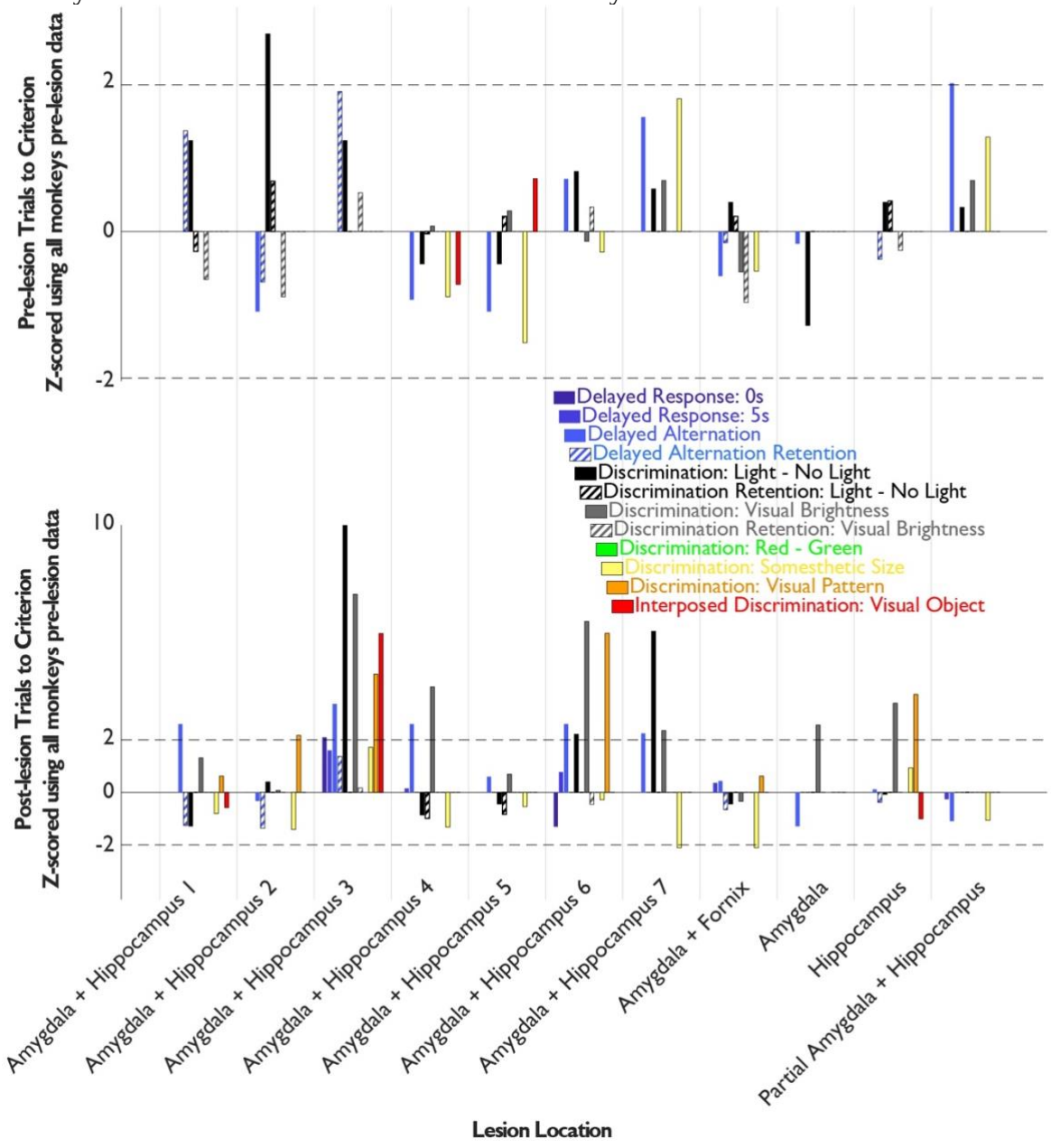

Figure 4. Results from Orbach, Cordeau & Rasmussen (1960).

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 2** and **Figure 3**.

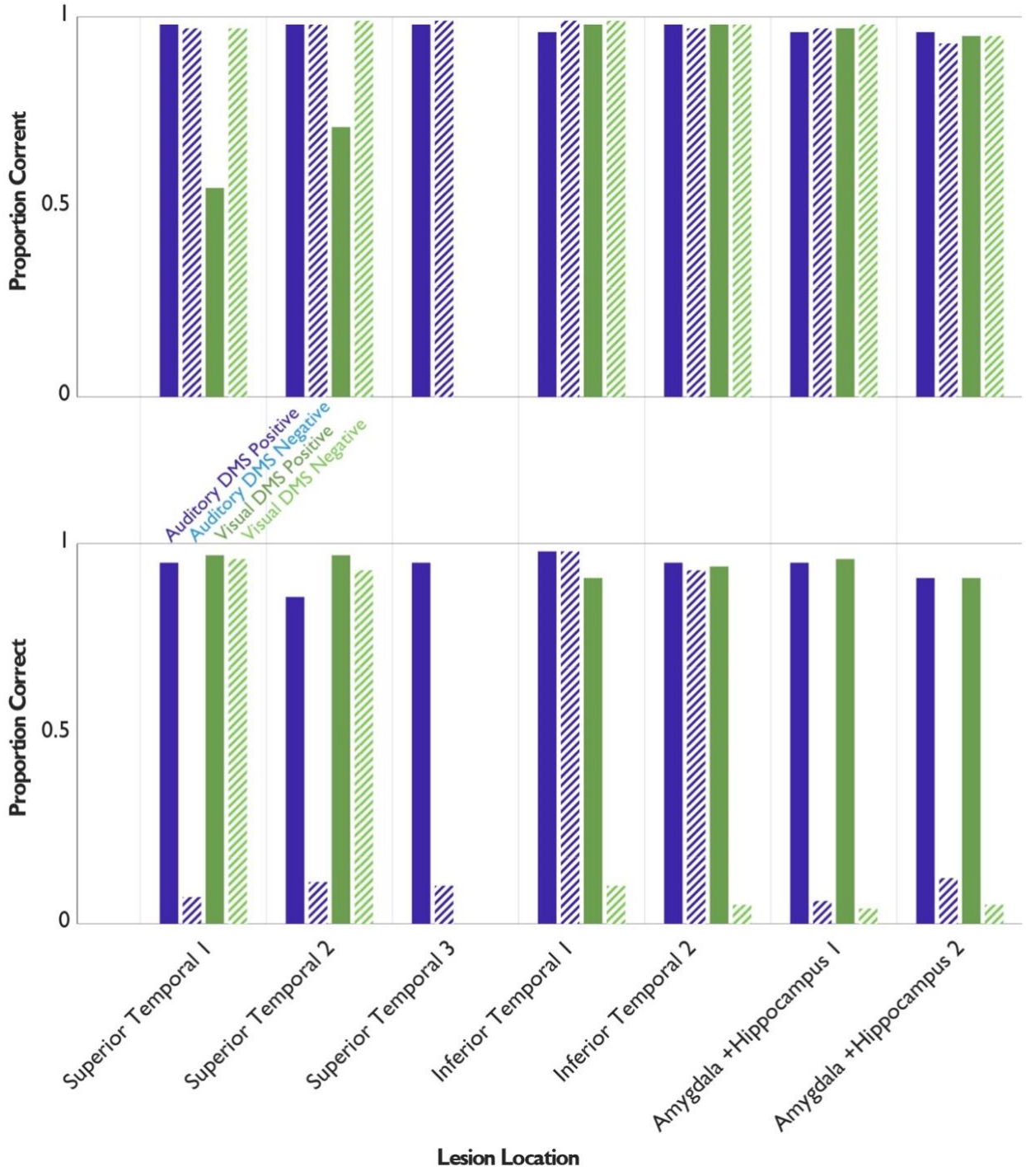

Figure 5. Results from Stepien, Cordeau & Rasmussen 1960

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 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 (Pribram et al., 1962). 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. Two of the control animals were then hippocampectomized and showed a retention deficit in the self-ordered task, but paradoxically 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 6**; 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. 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 before hippocampal lesion (Correll and Scoville, 1965; Drachman and Ommaya, 1964).

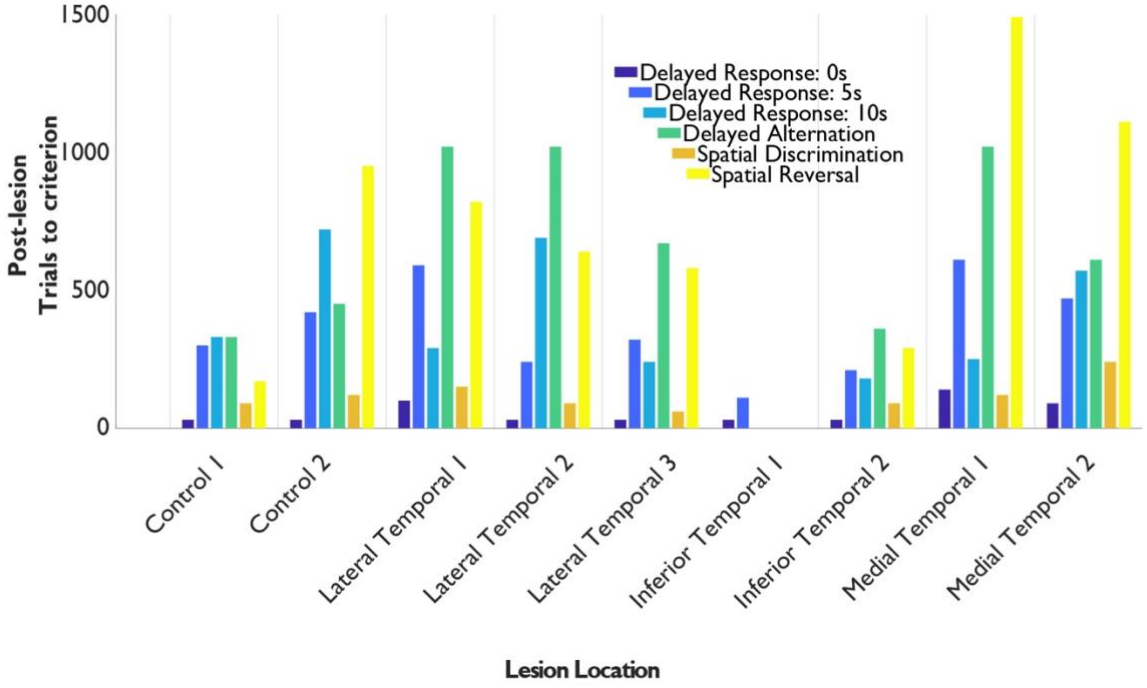

Figure 6. Results from Mahut & Cordeau (1963).

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

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.

SUMMARY

In the early 1960s, a lack of a clear nonhuman primate model of anterograde amnesia as seen in patient HM led some to speculate that the human hippocampus may be fundamentally unique in its organization and/or function. Hippocampal lesion studies were conducted in nonhuman primates, together with a variety of sensory discrimination, learning, and memory tests. It became increasingly common to test the effects of hippocampal lesion on tasks that required subjects to remember whether rewards were last observed under the left or right well of the WGTA; these were called "spatial tasks", and could include spatial discrimination, reversal, and alternation. In some cases, spatial deficits after hippocampal lesion were reported, though the data to support such claims are specious. An entirely unique set of electrophysiology studies were conducted in anesthetized and awake nonhuman primates. These showed that sensory information reaches apical dendrites of hippocampal pyramidal cells via the subiculum and entorhinal cortex, whereas interoceptive information is transmitted via septal inputs to basal dendrites.

THE 1970S

A NOTE ABOUT INFLUENTIAL STUDIES OF THE RODENT HIPPOCAMPAL ELECTROPHYSIOLOGY IN THE 1970S

Two primate lesion studies from the from the early 1960s showed deficits in 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 forms a cognitive spatial map of the environment, 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 of spatially-related activity in hippocampal neurons. The influence of this rodent work and resultant emphasis on spatial correlates of hippocampal activity persists to this day.

Notable lesion studies in the 1970s.

At least 14 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 employed two versions of a reversal task using a WGTA: an object reversal task, and a place reversal task (Jones and Mishkin, 1972). 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 performance 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, monkeys were trained on a "list" task, wherein objects are presented serially. Therefore, the number of objects and/or time intervening the reappearance of an object 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 7**; 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 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).

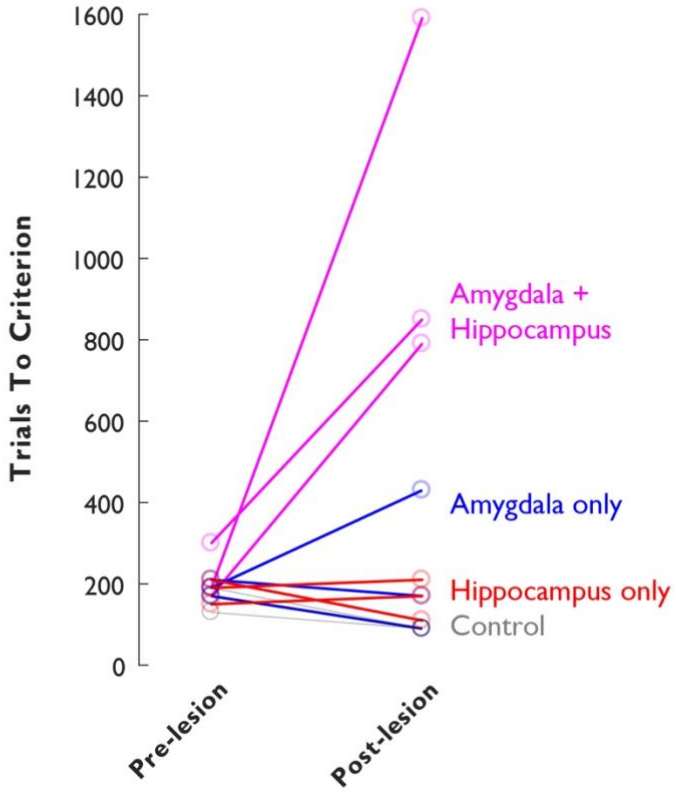

Figure 7. Results from Mishkin (1978).

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.

SINGLE NEURON RECORDINGS IN THE 1970S.

One early single-neuron electrophysiology study 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).

Summary

Throughout the 1970s, lesions involving the hippocampus were found to produce a variety of behavioural deficits. However, these lesions were seldom specific to the hippocampus. A series of studies continued to accumulate evidence that nonhuman primates with hippocampal lesions were perturbed in their ability to learn whether the right or left well of a WGTA was rewarded and to reverse these learned associations ("spatial deficits"). Many of these studies also included damage to the parahippocampal gyrus and other areas of the medial temporal lobe, complicating interpretations of these data. Furthermore, an influential model of global amnesia was published using a new kind of memory task in subjects with combined amygdala and hippocampal lesions. In this decade, nonhuman primate electrophysiologists also started to adopt the same sort of WGTA-style behavioural paradigms. These studies reported that certain proportions of hippocampal neurons respond to task events or task periods, such as stimulus onset, cue and test stimulus (mis)matching, and identities of particular stimuli. This trend of reporting proportions of neurons responsive to task parameters carries forward for decades to follow.

The 1980s

Notable lesion studies in the 1980s

In this decade, at least 50 lesion studies involving the hippocampi of monkeys were published. 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 that suggested more generalized reversal deficits, depending on the cognitive strategy employed by subjects (Gaffan and Harrison, 1984). However, another study by the same group purported to show that hippocampal damage perturbs spatial capacities through 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. Monkeys with hippocampal lesion showed a significant decrease in their ability to choose the object at the novel location; these deficits were not seen after amygdala lesion, and neither lesion affected recognition memory. Note, in the following decades, it was purported that the spatial deficits observed in these monkeys should be attributed to inadvertent damage to neighbouring brain regions, not the hippocampus.

Mishkin's interpretation of the "global amnesia" shown in a trial-unique DNMS 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 used later in neurophysiological studies.

In 1988, a re-analysis of the effect of selective hippocampal lesions was undertaken using more sensitive statistical analyses, showing that aspiration of the hippocampus resulted in impaired performance on DNMS tasks (Ringo, 1988).

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 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, respond when it later 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.

SUMMARY

In the 1980s, the focus on understanding the role of the hippocampus in spatial processing was carried forward from the previous decade. Some lesion studies purported that hippocampal damage affected performance in object-in-place memory tasks. Other lesion studies emphasized the function of the hippocampus in memory, using delayed non-match to sample tasks, especially when monkeys had to withhold responses after presentation of certain cue stimuli. Nonhuman primate hippocampal electrophysiology studies continued to adopt behavioural tasks seen in previous lesion experiments. These studies reported hippocampal neurons with firing rates that changed according to behavioural response contexts (move versus withholding movement), stimulus novelty, and stimulus location on a screen.

THE 1990S

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 in electrophysiology studies 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).

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.

SINGLE NEURON RECORDINGS IN THE 1990S

In the early 1990s, a burst of nonhuman primate electrophysiology studies were published. Several of these studies were completed by a group of researchers at Toyama University, with single datasets appearing across many publications. For example, to characterize spatial responsiveness in hippocampal neurons, monkeys were seated in front of an operant conditioning apparatus and tested using 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 space relative to the stimulus 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 (Tamura et al., 1990). These results were recapitulated across several other publications (Ono et al., 1991a; Tamura et al., 1992). In another set of experiments, monkeys were seated inside a motorized cab, and an auditory cue tone was played from a speaker behind them (Ono et al., 1993b). 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. These results were also described in other publications (Ono et al., 1991a; 1991b, Ono et al., 1993a). 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 one study, they noted that the firing rates of some hippocampal neurons change over the course of learning stimulus-response associations (Cahusac et al., 1993). In separate experiments, 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).

SUMMARY

Hippocampal lesion studies in the 1990s closely followed the established lines of research from the previous decade. However, the scope of this literature expanded, with new studies expanding the variety of reversal tasks used in combination with experimental lesions to the hippocampus and rhinal cortices. Several novel hippocampal electrophysiology experiments were conducted in nonhuman primates in this decade, and each experiment was

published many times. Generally, these publications looked at hippocampal responses to particular objects, auditory cues, and the location of these cues, finding some analogy with rodent literature. This decade also saw the introduction of "spatial view cells" to the literature, which are hippocampal neurons that are active whenever subjects are facing a certain part of the environment, regardless of their specific location.

THE 2000S

NOTABLE LESION STUDIES IN THE 2000S

By the beginning of this decade, at least 140 studies in primates employing lesions involving the hippocampus had been conducted in an attempt to infer neuropsychological function from observed deficits. 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 literature 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; and delay interval in DNMS tasks. However, limitations in 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 ibotenic 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. The sites of lesions were described with less precision — for a comparison of the labels used then and most currently to report boundaries of temporal lobe damage, see **Figure 8**. 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, it is argued that all previous studies conducted using a WGTA are misinterpreted, since allocentric or egocentric spatial strategies can be alternately used to solve them (Banta Lavenex and Lavenex, 2009).

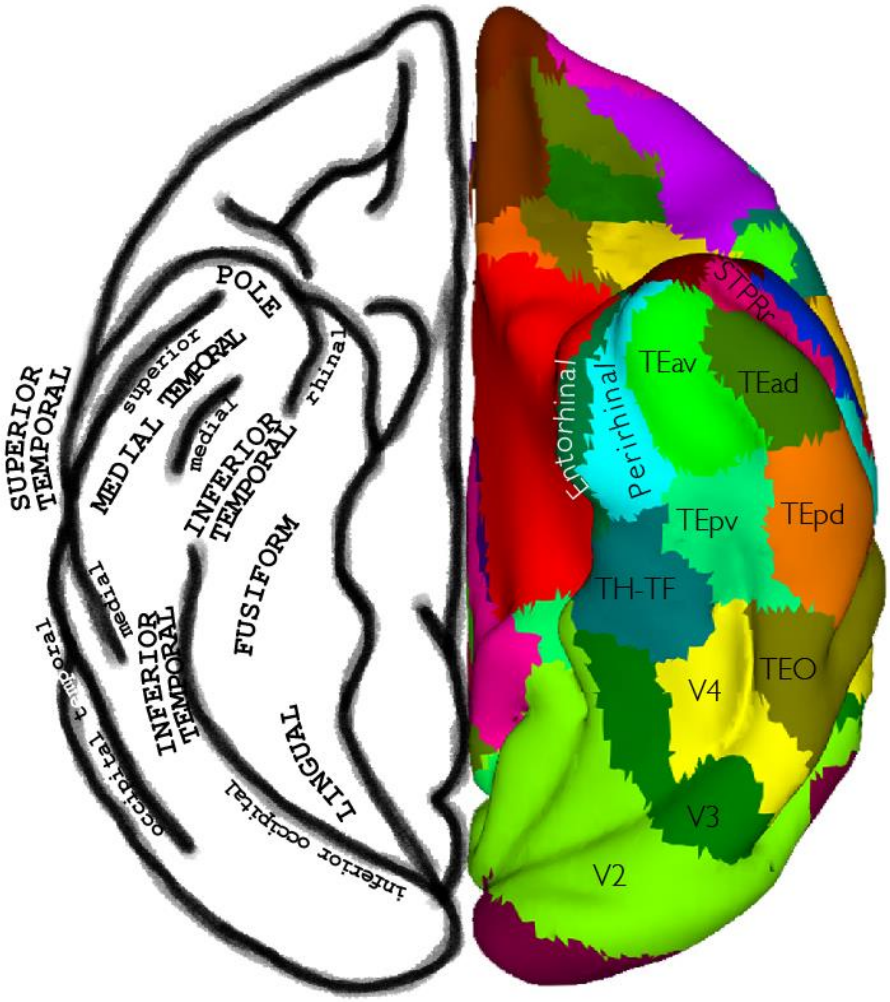

Figure 8. Surface anatomy of cortex surrounding the hippocampus

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).

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. The percentage of scenes and task periods where hippocampal neural activity changed as a function of learning was low relative 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).

SUMMARY

By the end of the 2000s, over 180 studies had been published involving some kind of lesion involving the hippocampus and some kind of behavioural testing. Comprehensive reviews and re-analyses of this literature were conducted, but with varied conclusions. In general, mid-20th century views on hippocampal involvement in sensory function or emotional regulation were ignored, with most emphasis on the role of the hippocampus in spatial learning, spatial reversals, or other memory function. The number of hippocampal single-neuron electrophysiology studies in nonhuman primates continued to expand, again focussing on characterizing the proportion of hippocampal neurons that seem to be modulated by spatial location (using both real and virtual movements), different behavioural task epochs, stimulus positions, and stimulus-response associations.

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 remained elusive through the 2010s. 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). Electrophysiology research also expanded considerably in this decade. No fewer than 32 original research articles featuring electrophysiological recordings in non-human primates were published in the 2010s.

Several of these studies focused on neural signatures of visual exploration and recognition memory in the macaque hippocampus. In one highly cited paper, 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. 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 during viewing of new scenes and repeated scenes that the subject recognized (that is, viewed for a shorter length than during initial presentation); a higher proportion than observed in

other recognition memory studies (Rolls et al., 1993; Xiang and Brown, 1999). A conceptually related task (without the behavioural assessment of recognition) showed that repeated viewing of scenes did not affect hippocampal firing rates, though the first and second image presentation was not compared directly (Thomé et al., 2012). A variant of this task included three categories of image presentation: novel images; "lure" images that were visually similar to the novel images (but not identical); and image repetitions (Sakon and Suzuki, 2019). In this task, hippocampal neurons recorded from the macaque dentate gyrus and CA3 could be used to classify all three image categories.

Visual exploration of natural scenes and recognition memory were also shown to have strong effects on hippocampal local field potentials (LFPs): high-frequency band LFP power was elevated and low-frequency band phase was aligned prior to fixation onsets during a visual search task (Hoffman et al., 2013). Another study recapitulated these findings, and observed elevated low-frequency band power prior to the presentation of images that would be recognized, only when monkeys would show behavioural recognition of the image (Jutras et al., 2013). High-frequency LFP events called sharp wave ripples occur during visual search (Leonard et al., 2015) and were more frequent prior to and during fixations on recognized images (Leonard and Hoffman, 2017). Scene recognition was also accompanied by pupil dilation and increased synchronization between high-frequency LFPs and hippocampal neuron activity (Montefusco-Siegmund et al., 2017).

Several studies during this decade focused on the nature of spatial representations in the macaque hippocampus. One of these papers included hippocampal recordings in freely moving macaque monkeys travelling through a narrow corridor, with 25% of CA1 neurons showing place-specific firing (Hazama and Tamura, 2019). Hippocampal neurons in marmosets navigating an L-shaped linear track also fired in a spatially-specific manner (Courellis et al., 2019). In this study, 14% of neurons showed place-specific firing patterns using a more conservative statistical threshold. These results are consistent with reports from rodent literature, but do not account for the effects of gaze and other aspects of behaviour on hippocampal neural activity. These effects were more closely examined in macaques navigating virtual reality environments.

In one virtual reality task, hippocampal activity was analysed during virtual goal-directed navigation (Wirth et al., 2017). 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 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). In subsequent experiments, macaques were trained to complete the same task in a variety of different virtual reality environments (Baraduc et al., 2019). Again, rather than specific claims about place-specific firing, these results emphasized that macaque hippocampal neurons were sensitive to task context and task epoch.

SUMMARY

In the 2010s, reviews of nonhuman primate hippocampal lesion literature sought a

definitive interpretation of previous hippocampal lesion studies; however, a singular consensus view was not found. Electrophysiology research saw remarkable growth, with at least 32 articles featuring electrophysiological recordings in non-human primates published during this decade. Several studies focused on neural patterns during visual exploration and recognition memory in the macaque hippocampus. Additionally, the influence of visual exploration and recognition on hippocampal local field potentials was investigated. High-frequency LFP power increased, while low-frequency phase was found to reset before fixation onset during a visual search task. Low-frequency LFP power was found to increase prior to recognized image presentations. Single-neuron representations of spatial locations were examined as well, in real and virtual environments. Neurons exhibited diverse tuning to factors like spatial position, gaze position, head direction, and task-related actions. Furthermore, experiments involving various virtual reality contexts reinforced the idea that macaque hippocampal neurons are sensitive to task context and epoch, rather than strictly adhering to place-specific firing patterns.

THE 2020S

In the 2020s, primate macaque hippocampal electrophysiology studies continued to report neural activity related to task epoch and behaviour, rather than pure spatial coding as seen in rodent studies. In one virtual reality study, monkeys were trained to use a joystick to navigate through a virtual reality environment and collect objects for reward (Gulli et al., 2020). While rodent-like spatial selectivity neurons were observed in each task, and hippocampal activity could be used to decode position in the virtual environment in each task **(Figure 9B**, Associative memory and Foraging). However, when a decoder was trained to classify position in the virtual environment using neural activity recorded during one task and tested using neural activity from the other task, the population code for space was not preserved and classification accuracy fell near chance (**Figure 9B**, Cross task). Importantly, it was shown that neurons recorded during the associative memory task that had spatial selectivity were better characterized as being selectively responsive to trial periods, objects in the virtual environment, rewards, or trial outcome feedback (**Figure 9C**). Therefore, previous studies that focussed only on spatial correlates of hippocampal firing may have incorrectly classify hippocampal neurons as responding to space or spatial view, when in fact they are coding specific sensory or mnemonic aspects of experiences. Hippocampal recordings in this task also showed phase-resetting aligned to saccades (Doucet et al., 2020), similar to reports during static scene viewing from the previous decade.

A role of hippocampal neurons in encoding behaviourally relevant stimuli and events was further supported by several studies using classical 2-dimensional psychophysical tasks. For example, in macaques performing a task that required context-dependent mappings of visual stimuli and operant responses, populations of hippocampal neurons were shown to encode context and reward associations, and to a lesser extent previous actions (Bernardi et al., 2020). Examining the activity of hippocampal neurons using a novel technique, it was determined that these representations of context and value were abstract and could support generalization behaviour in novel situations. In a task with dynamic reward values associated to visual stimuli, hippocampal neurons were shown to track the expected value of visual stimuli in an abstract manner (Knudsen and Wallis, 2021).

Evidence from freely moving macaques also showed complex spatial activity during a foraging task (Mao et al., 2021). Specifically, hippocampal neurons were shown to encode allocentric view in a head-direction-dependent manner more reliably than the monkey's position in space or gaze position in space.

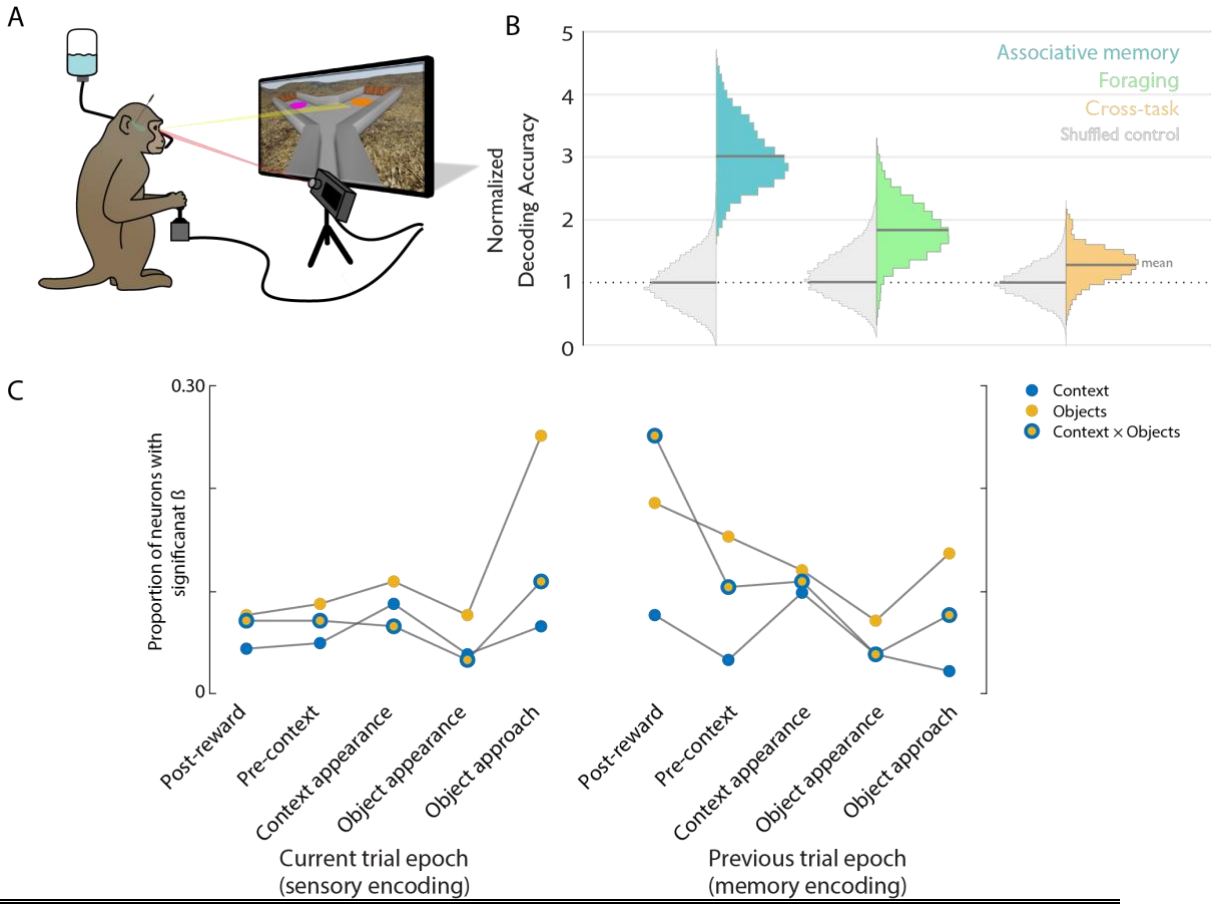

Figure 9. Summary of findings from Gulli et al. (2020).

A. Monkeys were seated in front of a computer monitor, and used a joystick to navigate through a virtual environment. During each session, single neurons were recorded from the right posterior hippocampus, and monkeys completed two tasks in the same virtual environment: an associative memory task, and a foraging task.
B. A population of neurons could be used to decode spatial position in the maze during both the associative memory task and the foraging task. However, when a decoder was trained using firing rate patterns recoded during one task, and tested using firing rate patterns from the other task, decoding accuracy fell near chance. These results show that the hippocampal population code for space was not preserved across tasks.
C. Neural activity during the associative memory task was related to sensory and mnemonic encoding of task periods, and trial-varying features such as context and objects present in the environment.

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

Despite the breadth of experimental paradigms and findings that have been covered to this point 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).

In the introduction of this chapter, we 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 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).

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 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 in Gulli et al. (2020). Their analyses suggests that not all neurons with place-specific activity change their contribution to spatial decoding across tasks. Since firing rates were scaled within tasks, 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, 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 had not been previously observed in the primate hippocampus.

THE HIPPOCAMPUS AND SPACE

The discovery of hippocampal "place cells" in rodents galvanized a movement towards electrophysiology in the hippocampus, and the belief that spatial location is encoded

as 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). These studies suggested that visual inputs may play a larger role shaping neuronal selectivities and processing in the primate hippocampus compared to rodents.

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. 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.

There are conspicuous differences between the spatial firing characteristics presented in the non-human primate electrophysiology literature, 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 primate studies 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).

Virtual reality studies can build upon these findings by examining single neuron and population codes for a single virtual environment across cognitive tasks. For example Gulli et al. (2020) 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, 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, these results suggest that 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).

A NEW APPROACH: NEUROPSYCHOLOGICAL VERSUS COMPUTATIONAL THEORIES OF HIPPOCAMPAL FUNCTION

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 results described throughout this chapter 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.

A comprehensive review of the literature throughout this chapter 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, or 2) record electrophysiological potentials in the hippocampus, and correlate them to the observation of the neuropsychological phenomenon. Non-human primate lesion studies appear to be falling out of fashion following their zenith in 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 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 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. A wealth of literature in rodents shows that 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 is 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, 2021). 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, 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 several studies (Brincat and Miller, 2015; Gulli et al., 2020). Indeed, a model of the hippocampus focused on sensory compression would generate sensory and mnemonic encoding as commonly reported in electrophysiology studies (Benna and Fusi, 2021). 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.

To maximize the effectiveness of the next generation of studies on hippocampal function, a few important lessons can be derived from successes and failures of past studies. 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; 3) recording from large populations of neurons across hippocampal subfields, and 4) determining possible differences between across species.

Conclusions

The goal of this chapter was to comprehensively summarize what we have learned about the function of the hippocampus by studying this brain area in non-human primates. Taking in this literature as a whole, over a span of nearly 70 years, researchers have conducted an incredible number of difficult, clever, and incisive task designs coupled with either lesion experiments or electrophysiology. However, these studies are not interpreted in a vacuum; instead, the recent trend has been to interpret findings from studies in non-human

primates with respect to neuropsychological theories from rodent-dominated or clinically-dominated literature (theories of spatial navigation or memory, respectively). New insights may come in a new era of hippocampal research in non-human primates, where the complex behavioural paradigms can be conducted, with rigorous control over and parameterization of experimental conditions. 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.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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