UNIVERSITY OF CALIFORNIA,
IRVINE

A role for pre-stimulus theta activity in the generalization of salient stimuli

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Mathematical, Computational and Systems Biology

by

Logan Davendra Harriger

Dissertation Committee:
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2021

DEDICATION

To

my family and friends

in recognition of their support

a motivation:

Rhythm imposes unanimity upon the divergent, melody imposes continuity upon the disjointed, and harmony imposes compatibility upon the incongruous.
-Yehudi Menuhin-

an apology:

Ars longa vita brevis
-Hippocrates-

and hope:

Success is the ability to go from one failure to another with no loss of enthusiasm.
-Winston Churchill-

TABLE OF CONTENTS

LIST OF FIGURES

FIGURE **PAGE**

LIST OF TABLES

TABLE **PAGE**

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To my family and friends, your love and support were a vital source of courage and inspiration to me.

VITA

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ABSTRACT OF THE DISSERTATION

A role for pre-stimulus theta activity in the generalization of salient stimuli

by

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Doctor of Philosophy in Mathematical, Computational and Systems Biology
University of California, Irvine, 2021
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The hippocampus's role in memory was first recognized in 1957 after the bilateral resection of patient HM's medial temporal lobes left him with profound amnesia; HM's case study supported hypotheses that the brain possesses multiple memory systems, and suggested the hippocampus is critical for memories of experience. Subsequent lesion cases bolstered additional support, but initially, experimental progress was limited by a lack of technology that could ethically probe hippocampal function in humans, and in animals, was confounded by flawed experimental design and sidetracked by a competing theory about the hippocampus's role in spatial navigation. Nevertheless, research on navigation became complementary, offering new experimental paradigms also suitable for probing hippocampal memory function and revealing many noteworthy features of hippocampal function like the theta rhythm. Today these research trajectories have begun to coalesce, and now prominent theories presume a more general role of the hippocampus as an index linking arbitrary cortical activation patterns; furthermore, these index representations are thought to relate to the ability of generalizing over or discriminating between similar stimuli via pattern separation/completion processes.

Brain electrophysiology is composed of a geometric progression of distinct rhythms, and the theta rhythm (3-8 Hz) has been elegantly linked to navigation processes in the hippocampus of various mammalian species. Additionally, this activity has been associated with memory in mammals, including humans, albeit, primarily with non-invasive methods incapable of attributing this activity to the hippocampus; notably, several studies have also demonstrated that pre-stimulus theta activity is correlated with recognition memory strength. Nevertheless, in the last couple of decades, direct recordings of human hippocampi have been conducted in patients implanted with intracranial EEG (iEEG) prior to brain surgery, but these studies related to memory have provided conflicting results, casting some doubt on the function of hippocampal theta.

In this dissertation, I analyze iEEG data collected from human epilepsy patients while engaged in a recollection memory task. I demonstrate that post-stimulus theta during encoding is indeed associated with successful recollection memory. While the first result runs counter to the several iEEG studies on memory, it is consistent with long-standing theories about theta's role in hippocampal memory processes. Additionally, I provide evidence that pre-stimulus theta activity at encoding is associated with poor recollection memory in the presence of mnemonic interference. Although this result also seems to be in contradiction with all prior accounts of pre-stimulus theta's effect on memory, it might be reconciled by interpreting the role of pre-stimulus theta as facilitating generalization of memory, rather than memory in general.

BACKGROUND

A brief history of the neurobiology of learning and memory

Unlike physics, which has great theories and is constantly in search for new tools to test them, neuroscience is still in its infancy, searching for the right questions..
- György Buzsáki-

The neurobiology of learning and memory is the study of how the brain, at various scales – from molecular biology to interactions between brain regions – forms, maintains, and transforms information about past behaviors, thoughts, experiences, etc. This discipline was born out of a fusion of two fields: neurobiology and the psychology of memory.

The brain has been studied since the time of the Egyptians c. 1600 BC, but besides gross anatomical descriptions and a few associations with disease, little about it was understood about the brain. After the 5th century BC, the belief that the brain was the origin of the mind slowly grew among the intelligentsia, but it did not become a popularly held belief, until the case of Phineas Gage was reported in 1848 AD. It could be argued that neurobiology first began with Luigi Galvani's observation that frog legs moved when stimulated by electricity and his theory that nerves moved electrical fluid to the muscles, but the realization that there was an electric potential across cellular membranes and that neurons exhibit spikes in membrane potential called action potentials did not come until ¾ of a century later (du Bois-Redmond, 1884; Galvani & Galvani, 1792; Matteucci, 1846; Piccolino, 2006). Before these neuronal mechanisms were discoveried, Jean Pierre Flourens had already begun lesioning the brains of rabbits and pigeons to examine their effect on behavior, representing a very early fusion of psychology and neurobiology, but not yet a study of memory (Flourens, 1825).

Psychology had been the business of philosophers and religious figures for millennia until Gustav Fechner pioneered the field of experimental psychology with his mentor Ernst Weber and began to overturn the dogma that the mind could not be studied quantitatively while introducing the Weber-Fechner Law: that the perceived change in a stimulus varies logarithmically with stimulus intensity (Fechner, 1860). Inspired by Fechner's book, Hermann Ebbinghaus pioneered the study of memory a few decades later, but perhaps due to the enduring dogma and a lack of intellectual support, he was his only experimental subject. His most significant work involved creating a lists of nonsense syllables and randomly drawing a subset to memorize; he studied them by reciting them to the standardized cadence of a metronome and then tested his recall over time to derive the rate of his learning and forgetting of these novel sounds, thereby introducing the influential concepts of learning and forgetting curves (Ebbinghaus, 1885). These early psychological studies showed that processes of the mind could be studied rigorously rather than just speculated on by philosophers, and thus established the foundations of experimental psychology.

A few years after Ebbinghaus's publication, a French psychologist, Theodule Ribot, observed that memory loss in his patients typically followed a sequential progression, now called Ribot's Law, whereby more recent memories were lost before older, more habitual and/or emotional memories; he also believed that brain pathology or injury was the cause of these conditions (Ribot, 1890). These insights were some of the first suggestions that the brain had multiple memory systems. William James also had several prescient insights about memory. Like Ribot, he suggested the existence of several memory systems functioning on different timescales; specifically, he postulated the existence of after image,

primary memory, and memory proper, which in today's jargon, roughly correspond to sensory, short-term, and long-term memory, respectively. He also believed that memory was a purely physical phenomenon of the brain, and introduced the indispensable notion of plasticity:

> *Plasticity…means the possession of a structure weak enough to yield to an influence, but strong enough not to yield all at once…[N]ervous tissue, seems endowed with a very extraordinary degree of plasticity of this sort; so…the phenomena of habit in living beings are due to the plasticity of the organic materials of which their bodies are composed.* (James, 1890)

Santiago Ramon y Cajal's work was formative to the study of cellular neurobiology, and although his studies were anatomical in nature, his speculation about functional consequences of anatomy was visionary. Using microscopy and staining techniques developed by Camilo Golgi, Ramon y Cajal made intricate diagrams of slices of bird brain and discovered this brain tissue was not a continuous reticulum of neurons as Golgi believed, but rather that neurons formed axonal-dendritic connections between discrete cells. He speculated that these connections, which Sir Charles Sherrington called synapses, could be a mechanism for neural plasticity (Ramón & Cajal, 1894). The debate about reticulum vs neuron theory between Golgi and Ramon y Cajal was heated, and Golgi never actually accepted the neuron doctrine, but nonetheless these scientists were jointly awarded the 1906 Nobel Prize in Medicine and Physiology for these seminal contributions to neuroscience.

Edward Throndike and Ivan Pavlov advanced the study of memory by pioneering animal models as a method to empirically study mnemonic phenomena. In Thorndike's dissertation he introduced the notion of operant conditioning by putting animals in a noxious environment (a small box), which they would eventually learn to escape (Thorndike, 1911). Pavlov on the other hand created the classical conditioning paradigm to

show that natural (unconditioned) stimulus-response associations like food and salivation could be hijacked by an inert (conditioned) stimulus; for example, preceding the presentation of food with the sound of a bell (Pavlov & Anrep, 1927). Although neither Thorndike nor Pavlov directly studied the brain, they introduced the idea of studying learning more quantitatively with experiments and showed that memory processes could also be studied in animals.

It was the work of Karl Lashley that finally fused the psychology of memory with neurobiology. Richard Semon had recently developed a theory of the "mneme": the linking of external stimuli to an internal state of the nerves that were encoded in some biological substrate, which he called an "engram", and Lashley attempted to find this engram by lesioning portions of a rat's cortex and evaluating how those lesions affected their ability to acquire or perform behavioral tasks (Lashley, 1929; Semon, 1921). Lashley eventually concluded that engrams were widely distributed over the cortex, which he called the principle of mass action, and that cortical tissue was equipotent, in other words remaining cortical tissue could eventually compensate for function lost from lesions (Lashley, 1951). His conclusions were slightly misguided by his crude methods, but because they exemplified the first foray into the neurobiology of memory, they left a lingering impact on the field.

Perhaps the most impactful discovery for the neurobiology of memory, arose from the case study of Henry Molaison, known as patient HM before his death (Scoville & Milner, 1957). HM suffered a bicycle accident when he was 7 years old, that is believed to have caused clonic-tonic epilepsy. His epilepsy steadily worsened with age and twenty years after the accident, his seizures had become so frequent and intense that he became a

candidate for resective brain surgery. His surgeon was William Beecher Scoville, who localized the seizures to both medial temporal lobes, and subsequently performed a bilateral resection of Molaison's hippocampi. Following the surgery, HM. suffered severe retro-anterograde amnesia and temporally graded anterograde amnesia. His life would never be the same, and nor would humanity's understanding of the neurobiology of learning and memory. Brenda Milner, who previously studied two other patients with amnesia due to unilateral resections of the medial temporal lobe, was invited to perform a psychological evaluation of HM; her studies revealed he had even more profound deficits than the others. HM could not recall new experiences for more than a few moments. However, HM did exhibit the ability to improve on motor tasks overtime, despite not recalling having ever practiced them before. Milner's account of HM, brought into question Lashley's theories of equipotency and mass-action, and started an entirely new research trajectory for the neurobiology of memory.

Studying episodic memory

There is no good reason to assume that the brain is organized in accordance with concepts of folk psychology.
- Cornelius H. Vanderwolf-

In the several decades following Milner's account of Molaison's amnesia, a tremendous effort has been focused on identifying the specific contributions of the hippocampus, and medial temporal hippocampal (MTH) system in general to memory but studying the brain in relation to a high-level psychological process presents a myriad of philosophical challenges.

The first challenge is just identifying the object of study: memory. The essence of memory could be defined as a persistent trace of the past, but such a general concept leaves

considerable room for the pervasive nuance of the natural world; psychologically, memories vary by timescale, level of conscious awareness, generality, etc., and the literature shows that there are distinct neurobiological systems and mechanisms supporting these various types. By generalizing the deficits and intact abilities of HM and other studies on memory, Endel Tulving proposed a distinction between explicit memories, which could be consciously recalled and verbally recounted, and implicit memory, which could not be expressed verbally and were recalled unconsciously (Tulving, 1972). He further suggested that explicit memories should be distinguished as episodic if they involved specific experiences, or semantic if they involved only general knowledge dissociated from experiences. This memory taxonomy has grown since and still remains the subject of some debate. So, memory, and cognition in general, is something of a moving target, evolving as the psychological constructs become better defined.

However, psychological constructs tend to have fuzzy, qualitative definitions that often make reference to other psychological constructs or subjective notions. This might be suitable for a clinician seeking to treat mental illness, but it impedes quantitative exploration with the scientific method. In attempt to address this shortcoming, a perspective known as behaviorism was adopted by many experimental psychologists in the first half of the 1900's. John B. Watson is credited with establishing the movement with an article called *Psychology as the Behaviorist Views It*, now commonly called "The Behaviorist Manifesto":

> *Psychology as the behaviorist views it is a purely objective experimental branch of natural science. Its theoretical goal is the prediction and control of behavior. Introspection forms no essential part of its methods, nor is the scientific value of its data dependent upon the readiness with which they lend themselves to interpretation in terms of consciousness. The behaviorist, in his efforts to get a unitary scheme of animal response, recognizes no dividing line between man and brute. The behavior of man, with all of its refinement and complexity, forms only a part of the behaviorist's total scheme of investigation.* (Watson, 1913)

Watson's intention was to give psychology a stronger scientific foundation by using behavior, which could be observed and measured, as opposed to the prevailing, but flawed, method of introspection, and secondarily, to emphasize what Thorndike and Pavlov had shown already: that studying animal behavior can be as informative as studying the behavior of humans. Although many pioneers such as Fechner and Ebbinghaus had already implemented this framework, Watson's formal proposal of this perspective ushered in a new era of more rigorous psychological studies. It was a valuable development, but this fixation on behavior began to limit the progress of psychological research.

Behaviorists believe animals inherit genes through the course of evolution, which in turn provide them with a brain programmed with a behavioral repertoire to adapt to its environment. They study their subjects by managing their environmental contingencies: their reflexes can be trained to be elicited with neutral stimuli (classical or respondent conditioning) and more volitional behaviors can be modified with positive or negative reinforcement, i.e., reward and punishment, (operant conditioning). While most behaviorists did appreciate the brain's relationship with behavior – for example, Watson's own dissertation examined the relationship between learning and brain myelination – subjects were essentially treated as a black box and there was an aversion towards studying or theorizing what might underlie behavior.

Fortunately, another paradigm shift began to take hold in the 1950's known as the cognitive revolution, which moved psychology away from its restrictive behaviorist principles. Intellectuals from various backgrounds such as linguistics, computer science, and neuroscience began to argue that behaviorism could not adequately characterize psychological phenomena. This interdisciplinary approach came to be known as cognitive science, and in direct opposition to behaviorism, its principal object of investigation is the mind. Cognitive science attempts to understand cognition in terms of how an intelligent system represents, processes, and transforms information; David Marr, a prominent cognitive scientist who was indispensable to research on the hippocampus and memory – among many things – described this philosophy as follows:

> *The three levels at which any machine carrying out an information processing task must be understood [are:]*
> ***Computational theory****[:] What is the goal of the computation, why is it appropriate, and what is the logic of the strategy by which it can be carried out*
> ***Representation and algorithm****[:] How can this computational theory be implemented? In particular what is the representation for the input and output, and what is the algorithm for the transformation?*
> ***Hardware implementation****[:] How can the representation and algorithm be realized physically (Marr, 1982)*

A central theme of cognitive science is the development of theory in the form of computational models of cognitive processes. This modeling framework was an important innovation because it provides a conceptual bridge between psychology and the brain. For instance, the psychological construct of episodic memory is conceptually distant from the activity of neurons in the medial temporal hippocampal system, so to truly understand this relationship more layers of abstraction are needed to bridge this gap. Such theoretical models serve to define the object of study more precisely and generate specific hypotheses to guide neuroscientific exploration.

Regardless of the epistemological perspective, another major philosophical issue in the study of the brain is ethics. For society to function, it must protect the rights of its members, and likewise, there are international agreements, national laws, institutional boards, etc. are in place to oversee and/or limit the scope of research on humans. The details of these safeguards are complex, but quite simply, as researchers, we seek not to do any harm to human subjects. Critically, this limits the invasiveness of measurements and of experimental design for research involving humans. Until the development of MRI and of source reconstruction techniques for EEG & MEG, this posed profound limitations on human brain research, as it was impossible to measure the activity of specific brain regions; therefore, the only way episodic memory could be studied in the human brain was the same way it was discovered: the serendipitous misfortune of a lesion to an individual's MTH. Several other lesion cases did arise and inform neuroscience; for example, three patients who suffered an anoxic-ischemic episode at a young age and were left with damage to the hippocampus but an otherwise intact medial temporal lobe – like HM, these patients had profound anterograde amnesia, but unlike HM, these subjects were able to acquire new facts, thus suggesting that the hippocampus is not necessary for semantic memory (Rudy, 2021; Vargha-Khadem et al., 1997). With the advent of non-invasive techniques to measure brain activity, episodic memory could be studied in the hippocampus, but the resolution is often coarse, and the experimental manipulations must be must be minimal. However, animals enjoy significantly fewer rights in society, which enables research to continue and advance.

While there are still protections for animals to prevent their abuse, neurobiological studies on animals typically involve mutilation, and experiments often terminate with the

subject's sacrifice. Today, this invasiveness of measurement allows scientists to probe the brain of animals at extremely high resolution, like the activity of single neurons, ion channels, or genes. This invasiveness of experiment allows scientists to precisely manipulate the subject and study phenomena that would be taboo in humans, like processes related to pain, sex, and even death; determine the mechanisms and effects of drugs; or create genetically modified animals to serve as models for disease. Early brain studies involved lesioning animal brains and observing the resulting loss of function. In the wake of HM, several such lesion studies were performed on rodents, rabbits, cats, and monkeys (Kimble, 1963; Mishkin, 1978; Peretz, 1965; Port et al., 1986). However, these early lesion studies did not show the expected dramatic deficits in memory that had accompanied HM's resection – probably for three reasons: (1) an incomplete description of HM's lesions, (2) poor surgical techniques, and (3) inappropriate task design. A post-mortem study of HM's lesion revealed than HM's lesions were much more extensive than originally believed, and rather almost two-thirds of his inferomedial cortex had been removed including portions of the entorhinal, parahippocampal, and piriform cortices in addition to the hippocampus and amygdala (Annese et al., 2014). In the animal studies, lesions were typically made only to the hippocampus, which produce significantly less pronounced effects to memory (Zola & Squire, 2001). Furthermore, these deficits to memory were largely undetectable in these animal studies because many tasks did not precisely test episodic memory. A prominent example of these shortcomings involved a recognition memory task in monkeys called the delayed non-match to sample task, whereby a stimulus is initially presented, and after a delay, the item is presented along with a novel one, and the monkey must choose the novel item to receive a reward. Importantly,

recognition can be facilitated by either recollection, which is hippocampal dependent, or a vague sense of familiarity, which does not depend on the hippocampus. In this study, monkeys with lesions to only the hippocampus or amygdala did not show a deficit on this task, but when lesions were performed on the hippocampus and amygdala together, there was a deficit in memory. There were two major criticisms of this study: first, was the fact that the task could be accomplished with familiarity memory, and second, later studies revealed that when both regions were lesioned together, poor surgical techniques actually caused widespread damage to the MTH (Brown & Aggleton, 2001; Rudy, 2021; Rugg & Yonelinas, 2003).

The failure of these early experiments motivates the discussion of another issue for biological research in general: the appropriateness of the experimental model. This issue is two-fold for cognitive neuroscience: (1) the cognitive task and (2) the subject. The cognitive task used in a study and the behavior it elicits entails an operational definition for the cognitive process being studied; for example, for the task used in this study (see *Methods*), correctly identifying targets as old and lures & foils as new, provides an operational definition for recollection memory, a type of episodic memory. So, some of the criticism of early work on episodic memory in animals were critiques on their operational definitions of episodic memory. If the task does not elicit the cognitive process in question, it seriously confounds the experimental interpretation. The subject is another important aspect of an experimental model. Research is generally geared toward its application to humans, but animals serve as a model for humans to allow more invasive experiments, but this is only a benefit if the model helps the experimenter learn something about what the model is intended to represent, in this case, [human] episodic memory. Translational

research has always been plagued by this issue because the biology of animals differs from humans in critical ways, and these differences increase with phylogenetic distance. For example, the hippocampus of rodents comprises a much larger percentage of their brain than humans, has a different neuronal composition, and differs in anatomical morphology and orientation. Cognition, which to a large extent is a product of biology, faces similar issues: each species through the course of evolution has developed a unique cognitive repertoire to survive and reproduce in its ecological niche, and their cognition might not be informative to humans.

Cognitive neuroscience is difficult to study in non-human animals, for the reasons discussed above, but these problems are is exacerbated by the very definition of episodic memory, which is given in terms that categorically prohibit its observation by a third-party (e.g. autobiographical, conscious, subjective, and experience). Simply put, one cannot access the conscious experience of another. In epistemology, this is known as the problem of other minds; it is certainly insoluble with our current science, but also arguably in principle. Nevertheless, solipsism has no utility, and is particularly problematic for research on memory. Although it may be theoretically impossible to access the experience of someone else, we can readily observe the similarities between ourselves and another human or animal, so from a rational perspective we can reasonably infer that other subjects are also endowed with a conscious experience. For people, a verbal report of their experience and their distinctive human mannerisms make this conclusion nearly indubitable; however, making similar inferences about animals who lack these familiar demonstrations becomes more difficult and again worsens with phylogenetic distance.

Trudging through these philosophical issues made early research into the neurobiology of episodic memory especially challenging, and while they continue to complicate progress, early pioneers created a foundation for today's researchers. Now there are strong epistemological frameworks, experimental paradigms, and a firmly established consensus that episodic memory requires the hippocampus, (Buzsáki & Moser, 2013; Eichenbaum, 2017; Squire, 2004).

Anatomy of the medial temporal hippocampal system

Anatomy is to physiology as geography is to history; it describes the theatre of events.
-Jean Fernel-

The medial temporal hippocampal system (MTH) is comprised of the hippocampal formation and the neighboring structures in the parahippocampal gyrus (Rudy, 2021). The hippocampal formation, or archicortex, is phylogenetically the oldest structure of the cerebral cortex. Its Grecian namesake derives from its bulbous, tortuous shape that when elongated resembles that of a seahorse. It encompasses the Cornus Ammonis (CA -- also known Ammon's horn due to this spiral shape or alternatively the hippocampus proper), dentate gyrus (DG), and subiculum. On the other hand, the laminar structure of surrounding parahippocampal gyrus is architecturally more similar to the neocortex and thus considered to be periallocortex, a tissue forming the transition between archicortex and neocortex. The parahippocampal gyrus includes the uncus, perirhinal, entorhinal,and parahippocampal cortex. The hippocampus, like the neocortex, is unique to mammalian species, but evolved from homologous structures present in earlier amniotes, known as the medial pallium. Although the hippocampus is often described as the medial temporal lobe,

its septal-amygdaloid (tail-head) axis was originally oriented dorsally beginning near the anterior commissure and extending posteriorly toward the midbrain. Through the course of evolution, it curled as it grew and migrated ventrally. In rodents, the hippocampus is described as having a dorsal (tail) and ventral (head) portion, but the hippocampus in humans has migrated even further ventrally, so our homologous regions are referred to as the posterior (tail) and anterior (head) hippocampus (Murray, Wise, & Graham, 2017).

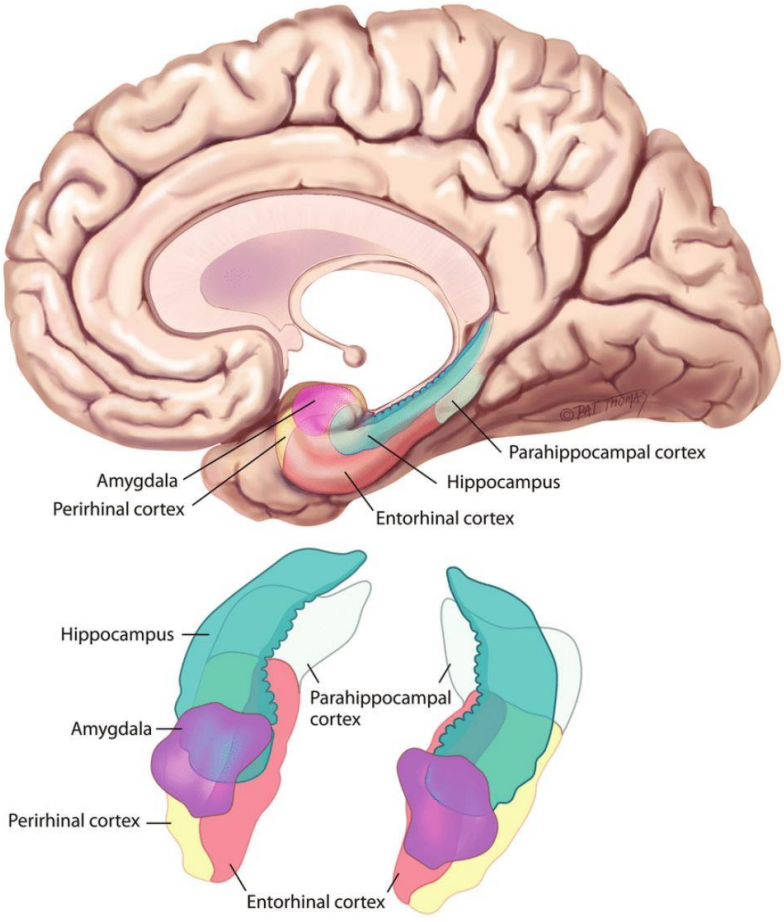

Figure 1: The medial temporal hippocampal system

From (Purves et al., 2008)

From a coronal perspective moving medially, the hippocampal formation extends out of the parahippocampal gyrus and spirals in on itself beginning with the subiculum, transitioning through CA1-CA3 subfields of the hippocampus proper to form a C-shape

bounded by the hippocampal fissure, and at the center of this spiral is DG, a C-shaped layer interlocking the adjacent C-shaped CA. The archicortex forms a majority of the floor of the inferior horns of the lateral ventricles. Following along these inferior horns from the anterior to posterior, the bulbous head of the hippocampus is adjacent to the amygdala and uncus; then continuing posteriorly toward the hippocampal tail, the grey matter of the hippocampus tapers as it approaches the corpus callosum and diverges from a white matter tract called the fimbria into a thin layer of grey matter known as the gyrus fasciolaris, which continues on to an even thinner layer directly above the corpus callosum and below the cingulate cortex known as the indusium griseum. The fimbria emerges out of CA3 in the coronal aspect, and from a sagittal perspective follows the lateral ventricles adjacent to the choroid plexus. As the fimbria diverges from the grey matter it becomes the fornix and the two hippocampi converge medially joined by the commissure of the fornix. The fornix forms the inferior medial portion of the partition between the left and right anterior horns of the lateral ventricles, known as the septum pellucidum, and is superior to the third ventricle where it contacts the tela choroidea. As the fornix continues anteriorly, the left and right fiber tracts bifurcate to fork around the anterior commissure forming two columns: the postcommissural columns continue anteriorly to terminate on the medial septal nuclei, while the precommissural columns curl inferiorly following the third ventricle and terminating on the mammillary bodies (Murray, Wise, & Graham, 2017).

The proximity of the hippocampus to the lateral ventricles is noteworthy because during development the cell population lining the ventricles, known as the ventricular and subventricular zones, are the source of neural stem cells that will form the forebrain. Furthermore, the subventricular zone as well as the subgranular zone of the dentate gyrus

are the only regions known to continue neurogenesis into adulthood (Altman, 1962; Toda et al., 2018). There is some evidence that this sustained neurogenesis is an important contributor to the memory abilities of the hippocampus, serving to increase or maintain the capacity of the DG to support memory demands over an animal's lifetime (Yassa & Stark, 2011). However, even if neurogenesis is vital to memory, it is the intrinsic architecture and connectivity of the MTH that provides the substrate for the neuronal interactions underlying memory.

The allocortex sits between the basal ganglia, sometimes referred to as the "lizard brain," and the neocortex mediated by the periarchiform cortex. Both the neo and periarchiform cortex have a 6-layer structure with a very regular cellular architecture that is functionally segregated into local modules of neurons spanning the layers. These modules respond to particular statistical regularities in their input; at one extreme a cortical module may parse direct sensory inputs -- for example, responding to sonic frequencies or visual edges -- and on the other extreme it may integrate input from many other modules to represent more abstract concepts -- for example, responding to numbers or people. The majority of the cortex projects to the periarchiform cortex, i.e., the parahippocampal, perirhinal, or entorhinal cortices, which integrate and transform these heterogeneous cortical inputs into a sparser relational output -- or in the parlance of cognitive science, create "conjunctive representations" of diverse multiperceptionary inputs (Buzsáki, 2006). The EC, in turn, is the primary input to the hippocampus, so the hippocampus sits at the apex of conjunctive cortical representations.

The EC is the first node of the trisynaptic circuit, first described by Ramon y Cajal, and involving the three excitatory connections between EC, DG, CA3, and CA1 (Ramon y

Cajal, 1911). Layer 2 of the EC, is the principal projection to the hippocampus innervating both CA3 and DG via the perforant path. The granule cells of DG also innervate a majority of CA3 neurons, with a preference for those located closest to it in the hilar region, or the portion of CA3 that is enclosed by the C-shaped DG. Unmyelinated mossy fibers from these DG cells form only about 20 synapses each, but these large, "detonator synapses" are capable of discharging a CA3 pyramidal cell with a single action potential. In contrast, CA3 neurons primarily project to other CA3 neurons via recurrent collaterals. Moreover, the pyramidal cells of CA3 are large extending over two-thirds of the hippocampal volume and each neuron forming around 35,000-90,000 synapses with other CA3 cells (around a third of these reach the contralateral hippocampus), so this connectivity approximates a random graph - this characterization is also justified functionally because the firing of hippocampal cells evoked by different stimuli are distributed randomly throughout the hippocampal volume (O'Keefe and Dostrovsky, 1971;Harris et al, 2003; Buszaki, 2006). Finally, the principal cells from CA3 also project to CA1 via the Schaffer collaterals to complete the trisynaptic circuit. Note that CA2 is rarely discussed in this literature, but it is not easily distinguishable from the surrounding subfields (Maire et al, 2013). Another subdivision CA4 also used to be common but is now typically referred to as hilar CA3. Finally CA1 outputs this hippocampal activity back to the cortex via sequential relays from the subiculum, to layers IV and V of the EC, to the adjacent perirhinal and parahippocampal cortices of the parahippocampal gyrus, and then to the rest of the neocortex.

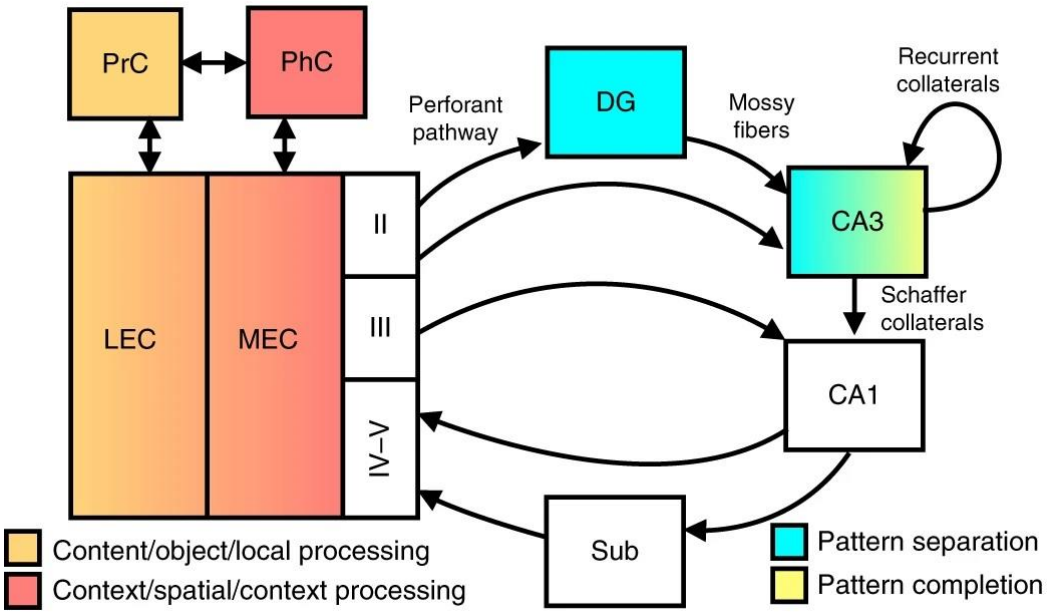

Figure 2: Tri-synaptic circuit of the MTH

From (Leal & Yassa, 2018)

The main anatomical themes for the medial temporal hippocampal system are (1) the diverse, conjunctive input from neocortex, (2) increasing representational sparsity, especially from DG to CA3 and CA3 to CA1, (3) the recurrent, small-world, and pseudorandom connectivity of CA3 creating a large representational space ideal for encoding sequences of arbitrary patterns, and finally (4) the reciprocal output of the MTH back to the neocortex via EC. These anatomical themes helped inspire the computational theory of pattern separation/completion as we will see in *Theoretical neuroscience of explicit memory*.

Brain electrophysiology

You have no idea, how much poetry there is in the calculation of a table of logarithms.
-Karl Friedrich Gauss-

The cellular architecture and connectivity of the brain permits and constrains the neural interactions underlying cognition, and these interactions likewise exhibit structure in their dynamics. This dynamic structure is manifested as rhythmic activity described in terms of its central frequency. Rhythmic activity was first noted in electrical recordings of rabbit cortex, but Hans Berger, the inventor of EEG, named the first of these such patterns in humans the alpha wave -- an intermittent 8-12 Hz signal over the occipital cortex increasing in power and duration when the subject closes their eyes (Beck, 1890; Berger, 1929). Since the discoveries of Beck and Berger, brain rhythms have been demonstrated to form a geometric progression from around 0.02-600 Hz in multiplicative steps of $e \approx 2.718$ (Buzsáki & Draguhn, 2004; Penttonen & Buzsáki, 2003). This collection of brain rhythms can be observed, to varying extents, in nearly all brain regions, it has been demonstrated in numerous mammalian species and presumably present in all, and some rhythms have been observed in non-mammalian species as well (Buzsáki et al., 2013; Shein-Idelson et al., 2016). Moreover, faster rhythms often co-occur at a specific phase of slower ones forming more complex nested structures analogous to the harmony of a musical chord. The literature correlating brain rhythms to physiological and cognitive processes is vast and growing rapidly. Today, brain rhythms are believed to constitute a hierarchical dynamic structure helping to orchestrate neuronal firing, and likewise they provide an essential framework for studying the electrophysiology of cognitive processes; some have referred to it as a neural syntax.

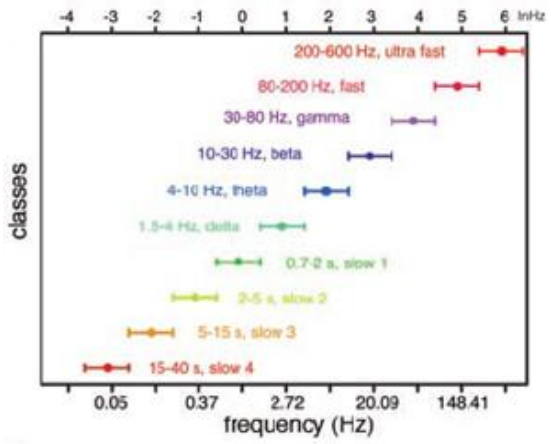

Figure 3: Rhythms of the brain

From (Buzsáki & Draguhn, 2004)

There are numerous mechanisms supporting brain rhythms from the cellular to population levels. At the cellular level, neurons exhibit membrane potential resonance (MPR), meaning they have natural frequencies of activation (Buzsáki, 2006). This resonance is due to the particular mosaic of ion channel proteins embedded in each cell's membrane, the various activation parameters of the channels, and how these channels are distributed over the cell's specific morphology. Some channels are always open or "leaky", constantly allowing ions to passively diffuse through them as the resting electrochemical gradient is reestablished; other channels open in response to the binding of a ligands – like glutamate and other neurotransmitters; and still others change their state depending on membrane voltage. Furthermore, many of the channels that change state involve active transport, i.e., require energy to move ions against the electrochemical gradient (Llinás, 1988).

These channels establish concentration gradients that drive ionic flux across the membrane. Due to the high intracellular concentration of negatively charged anions -- primarily amino acids and proteins -- neurons have a negative resting potential forming a

gradient directing positive ions intracellularly. The concentration of K^+ ions is high in the cell, while Na^+, Ca^{2+}, and Cl^-, are low, so the concentration gradient is also primarily directed intracellularly; however, an active sodium-potassium channel pumping two K^+ into the cell in exchange for three Na^+ out of the cell maintaining a low intracellular concentration of sodium and high concentration of potassium. Together these channels comprise a nonlinear dynamical system of ionic conductance and capacitance over the surface of the membrane, which controls the electric potential between the extra and intracellular space separated by the membrane. Like many dynamical systems, the balancing between energy transfer and storage imparts natural frequencies of operation called resonance. Resonant systems exhibit an amplified response to stimulation at their natural frequencies, and tend to transform energy inputs into output at their natural frequencies.

For instance, consider the simple resonance of a mass-spring system. When the spring is slightly compressed, the kinetic energy of the push compressing is converted to potential energy in the spring; by releasing the spring, the potential energy is again transformed into kinetic energy as the mass moves forward, but once the spring begins to stretch past its stable conformation, the kinetic energy begins to be stored as potential energy once again. Mass-spring systems exhibit resonance due to the intrinsic spring constant and mass of the system, so it will continue to oscillate between kinetic and potential energy at its natural frequency until all energy is eventually lost to heat or some interfering force. Likewise, if the system is stimulated at its resonant frequency, e.g., push/pulled at the moment all energy is stored as potential energy, its oscillations will be amplified. Similarly, randomly hitting the spring will induce displacements from the kinetic

energy of each impact that will be stored in the spring, and like before, induce oscillations in displacement as the energy is converted between potential and kinetic energy at the system's natural frequency; however, it will exhibit an additional noisy component from each random hit and the constructive or destructive interference it imparts.

Analogously, if a presynaptic neuron releases excitatory neurotransmitters, they will probabilistically bind to and open ligand gated channels on the postsynaptic neuron causing a brief ionic current into the cell. As the ions accumulate inside, the cell's voltage will increase before ion concentration gradients direct the ions back out of the cell through leaky channels to reestablish resting voltage; then, as charge accumulates outside the cell, the electric potential will again shift, thus creating subthreshold oscillations like the mass-spring or more appropriately an LRC circuit. Furthermore, if the postsynaptic currents are timed appropriately, the MPR will amplify these oscillations.

However, a neuron is much more complex than a spring: the multifarious channels with their specific activation parameters can endow single neurons with multiple resonant frequencies that depend on its state and local environment. For instance, an action potential is elicited by a moderate depolarization which opens Na^+ channels and causes a greater depolarization that will eventually lead to inactivation of the Na^+ channel and the opening of K^+ channels to stop depolarization and repolarize the cell. Additionally, hyperpolarizing a cell can open Ca^{2+} channels which will lead to a depolarization near the threshold of action potentials leading to much more significant sub-threshold oscillations. Moreover, since charge diffuses throughout the cell, the morphology of the cell can affect resonance -- similar to the way a room's shape determines its acoustic resonance -- and inhibition can shunt targeted portions of the cell, effectively changing its morphology

(Buzsáki, 2006). Finally, the presence of neuromodulators, the down/up-regulation of channels, and other mechanisms can retune the cell's resonance features.

Membrane channels determine how a neuron responds to changes in voltage and endow it with intrinsic frequencies of operation, but brain rhythms are a macroscopic phenomenon involving populations of interacting neurons. The natural frequencies give neurons a propensity to couple with other neurons at these frequencies, so resonance creates a dynamical foundation for the emergence of brain rhythms.

Neuronal circuits provide another mechanism for rhythm generation. Inhibitory cells are one reason neurons do not resonate out of control, so the feedback between excitation and inhibition can stabilize resonance, but it can also produce distinct oscillatory behavior. Inhibitory neurons tend to form large, low latency networks supported by gap-junctions (intracellular connection which allow cytoplasm along with ions to pass between cells) with other inhibitory cells; thus inhibition can spread widely and quickly to synchronize a large population of excitatory neurons(Buzsáki, 2006).

The theta rhythm in medial temporal hippocampal system

Before the functional importance of the hippocampus was known, a slow, rhythmic pattern ~5 Hz had been documented in the hippocampus of rabbits (Richard Jung et al., 1938). Another early study made several interesting observations about this pattern that would later be called the theta rhythm (Green & Arduini, 1954). First, the theta rhythm was observed in several MTH regions, 100 Hz electrical stimulation of several regions (including the tectum, thalamus, hypothalamus, preoptic area, and septum) evoked hippocampal theta; this rhythm was present in absence of the neocortex, but disrupted by

lesions to the septum or ipsilateral fornix and by administration of anesthesia. Second, theta was observed in response to olfactory, auditory, visual, and tactile stimuli and attenuated with habituation. Third, the hippocampi of rabbits, cats, and monkeys, all exhibited the theta rhythm; however, the theta rhythm was weaker and shorter in duration for monkeys. Finally, there was a relationship between neocortical and hippocampal EEG; typically, neocortical EEG was desynchronized during hippocampal theta waves.

The theta rhythm is ubiquitous throughout the MTH, but it is strongest and most regular in the portion of CA1 adjacent to the hippocampal fissure, known as stratum lacunosum-moleculare. It is also present in other limbic structures such as the amygdala and cingulate cortex, and although rhythms with similar frequencies are also present in various cortical structures, cortical theta is thought to be distinct from hippocampal theta (Buzsáki, 2002).

A mechanistic account for the generation of the theta rhythm has been sought since it was first reported when it was also shown that lesions of the septum completely abolish the theta rhythm throughout the HMS (Green & Arduini, 1954). The ablation of the theta rhythm is more specifically accomplished by lesioning the medial septum-diagonal band of broca (MS-DBB), and this phenomenon has been replicated many times over. However, while MS-DBB is necessary for the in vivo theta rhythm, the classic septal pace-maker provides an incomplete mechanistic account of theta (Buzsáki, 2002). There also appear to be at least two distinct theta channels first distinguished pharmacologically, atropine-resistant theta and atropine-sensitive theta (Kramis et al., 1975). Atropine-resistant theta is thought to depend on septal relays in layers II and III of EC targeting CA3 and CA1, respectively; furthermore, because all theta is abolished with co-administration of

ketamine with atropine, NMDA receptors are suspected to play a critical role. On the other hand, as the name suggests, atropine-sensitive theta depends on muscarinic activation by acetylcholine, and seems to depend on the recurrent network of CA3. In fact, a hippocampal preparation isolated from MS-DBB and the rest of the brain still exhibits spontaneous intermittent theta waves when bathed in a muscarinic agonist. Theta has also been described as a travelling wave (Jesus Hernandez-Perez et al., 2020; Leibold & Monsalve-Mercado, 2017; Osan & Ermentrout, 2001; Zhang, 2018).

Spatial navigation

Nothing in biology makes sense except in the light of evolution.
-Theodosius Dobzhansky-

Research on the cognitive function of the hippocampus has largely followed two themes: (1) explicit memory and (2) spatial navigation (Buzsakí, 2019; Buzsakí and Moser, 2013). As previously discussed, much of the first theme followed from lesion induced amnesia cases in human patients, and these striking cases motivated intense efforts in animal studies – primarily rodents – since their brains could be manipulated experimentally, and findings in animals eventually introduced the second theme. Due to the crude electrophysiology methods of the time, initially these rodent studies involved the assessment of behavior following targeted lesions. A typical outcome following hippocampal lesions in rats was hyperactivity and difficulty suppressing previously learned behaviors, and this led to the hypothesis that the hippocampus acts as an inhibitory control system for behavior and plays a central role in anxiety (Douglas, 1967; Kimble, 1968). Eventually, improvements in single unit recording techniques allowed rats to remain mobile during recordings, and in the wake of this development the spatial

navigation theme emerged from John O'Keefe's lab. In the first paper showing evidence of spatial dependence of neuronal firing, he took direct aim at the inhibition/anxiety hypotheses on the hippocampus:

> *Rats with hippocampal damage are reported to be hyperactive in novel environments, 'perseverative' and resistant to extinction on tasks that they have learned, heedless of drastic changes in their environment, and poor at spatial tasks such as mazes and tasks which require the alteration of responses on successive trials. These deficits could be due to the loss of the neural system which provides the animal with a cognitive, or spatial, map of its environment. (O'Keefe & Dostrovsky, 1971)*

The paper was just a short communication characterizing 72 units recorded from the CA1, CA3, or DG across 36 rats. Interestingly, they reported that several units showed theta activity while orienting, walking, sniffing, and bar pressing, as well as many which did almost nothing; however, most importantly there were 8 units which displayed reliable firing modulated by the animals' proximity to a specific location as they were coaxed into walking along several specific trajectories. O'Keefe and his colleague Lynn Nadel had been inspired by the theory of cognitive maps introduced by Edward Tolman, and in honor Tolman's ideas, they formalized their own theory of hippocampal function with a book called, *The hippocampus as a cognitive map* (O'Keefe & Nadel, 1978; Tolman, 1948). After some follow-up studies by O'Keefe's lab, a few similar demonstrations from other laboratories, and the publication of O'Keefe and Nadel's book, the inhibition/anxiety hypothesis on the hippocampus began to fall out of favor in the late 1970s as it quickly became overshadowed by research on spatial navigation.

Several years later, O'Keefe's graduate students, May-Britt and Edvard Moser, discovered a related phenomenon in the medial entorhinal cortex: grid cells (Hafting et al., 2005). Like the hippocampal place cells, grid cells show firing rate modulation related to space. However, these cells do not respond to a single location; instead, their firing rate

approaches a maximum in several regularly spaced locations that can be closely approximated with the vertices of an equilateral triangular grid, and which completely tiles the animal's immediate environment. The discovery of place and grid cells was so influential that O'Keefe and the Mosers were awarded the 2014 Nobel Prize in Physiology or Medicine.

More recently, just as the inhibition/anxiety hypothesis was absorbed by the superior explanatory power of the other two theories, there has been an effort to unify the spatial navigation theory under a more general framework that includes explicit memory (Squire, 1992; Burgess et al, 2002; Buckner & Carrol, 2007; Hasselmo, 2012; Buzsaki & Moser, 2012). This unification is motivated by the recognition that the phenomena of place and grid cells in navigation are analogous to those of episodic and semantic memory, respectively, and it is supported by a multitude of empirical data. Place cells in the hippocampus fire maximally in a given location, and during the traversal of an environment, place cells mapping adjacent locations fire sequentially, synchronized by the troughs of each theta cycle, such that the place cell representing the rat's current location fires at the minimum of the trough, and cells mapping those locations just recently traversed and those that will be subsequently traversed fire during the early phase and late phase of the trough, respectively. When the rat arrives at the next location, the firing of place cells is shifted in time in a phenomenon known as phase precession, which was also discovered by O'Keefe's lab (O'Keefe & Recce, 1993). Furthermore, the velocity of the rat modulates this relationship. In a one-dimensional environment, e.g. an elevated track, a place cells fire at their associated locations in a direction specific manner, e.g. only during a left-to-right traversal, while a different population of cells fire at the same locations for the

reverse direction. This sequential specificity is analogous to the sequential nature of an episodic memory. Now the prevailing thought is that episodic memory evolved out of mechanisms related to spatial navigation (Buzsáki, 2005; Buzsáki & Moser, 2013).

Theoretical neuroscience of explicit memory

Knowledge is not a series of self-consistent theories that converges toward an ideal view; it is rather an ever increasing ocean of mutually incompatible (and perhaps even incommensurable) alternatives, each single theory, each, fairy tale, each myth that is part of the collection forcing the others into greater articulation and all of them contributing, via this process of competition, to the development of our consciousness.
-Paul Feyerabend-

In his mid-twenties, David Marr published a series of three papers outlining ambitious theories for how the cerebellum, neocortex, and hippocampus, stored and processed information, respectively (Marr, 1969, 1970, 1971). These papers blended mathematical formalism with contemporary knowledge about brain anatomy to synthesize a computational theory about cognitive processes. One of his major contributions, known as pattern separation, has profoundly influenced how the hippocampus and episodic memory are studied today.

Marr first described a pattern separation computation in *Theory of cerebellar cortex*. He proposed that the granule cells of the cerebellum, which have sparse outputs and greatly outnumber the mossy fibers of the pontine nuclei that project to them, essentially filter the noisy combinations of their mossy fiber input. The crux of this idea is that transforming many inputs to a sparse output in a high dimensional network facilitates the discrimination of similar input patterns, and such a process could enable the cerebellum to refine noisy motor signals into well-orchestrated commands that are ultimately sent to muscles to generate coordinated movement.

Marr introduced a similar pattern separation process for the hippocampus in *Simple memory: a theory for archicortex* (Marr, 1971). In the introduction, he set up his paper as a kind of a sequel to his previous paper on the neocortex, in which he theorized that the relatively uniform tissue of the neocortex was composed of countless "classificatory units" hierarchically increasing in cognitive complexity from initial sensory input to abstract ideas which were eventually learned when something "became worth forming a special description for." Whereas he postulated that the six-layer architecture of the neocortex enabled these increasingly complex transformations of information, he argued that the hippocampus with its relatively simpler architecture was capable of "only a simple memorizing function" of an animal's "current internal description," essentially, the brain's activation pattern at a particular moment – a statement that resonates greatly with today's conception of the complementary learning systems of the MTH and neocortex. Using his mathematical formalism and referencing the hippocampal anatomy, he described how a process similar to the one in the granule cells of cerebellum could operate in the DG and CA subfields of the hippocampus to allow pattern separation of these simple memories and allow sufficiently different internal descriptions to be encoded with orthogonal neural representations. In addition, he introduced a complementary idea, now referred to as pattern completion, in which a sufficiently similar internal description, rather than be encoded distinctly, would instead trigger the retrieval of previous stored memories.

Marr's theory and conjecture has propelled, and in many ways anticipated, the following half-century of research into the hippocampus, but it did not have an immediate impact. The majority of research on the hippocampus during the 70's and 80's was focused on trying to characterize the effects of hippocampal lesions in rodents and largely followed

the spatial navigation research trajectory. However, Marr's theories were revisited by a few neuroscientists with expertise on the hippocampus, who simplified Marr's mathematical formalism by introducing a visual matrix representation of the pattern separation/completion computations (McNaughton & Morris, 1978). Unfortunately, Marr passed away from complications with leukemia in 1980 at the young age of 35, and he would not witness the legacy that became of his work. In the 90's his hippocampal theories began to resurface and began guiding empirical work. It was shown that the granule cells of the DG did appear to encode sparse representations (Jung and McNaughton, 1993). Even Marr's conjecture that the hippocampus might replay memories during sleep gained empirical support (Wilson and McNaughton, 1994).

A complementary research program began to reemerge called connectionism, which utilizes artificial neural networks (ANNs) as models for the brain. The first ANNs, called perceptrons, were introduced in 1958, but were quickly abandoned, when it was shown that they could not learn simple XOR programs unless the network utilized multiple layers combined with the fact that there was not an effective algorithm to train multilayer ANNs (Minsky & Papert, 1969; Rosenblatt, 1958). However, a breakthrough was made with the backpropagation algorithm, which enabled multilayer ANNs to be trained, and thus opened many new areas of research including connectionism, and eventually brought neural networks to the forefront of artificial intelligence research (Rumelhart et al., 1986). Although many experts have argued that ANNs were biologically implausible and could not aid in understanding the brain, others believed that, despite their major simplifications, ANNs could be designed to sufficiently capture the critical features of the brain that they could inform neuroscience (O'Reilly & Rudy, 2000).

In 1995, these ideas coalesced among an interdisciplinary group of scientists who synthesized a review paper composed of clinical observations in humans, empirical data from animals, neuroscience theory, connectionist modeling, and well supported conjecture. The paper elucidated several converging research programs and became a major influence on how neuroscientists collectively viewed the existence of "complementary" learning and memory functions of the hippocampus and neocortex (McClelland, McNaughton, and O'Reilly, 1995). It was inspired by the theories of Marr & Squire, and it bolstered these perspectives with new empirical data combined with results from connectionist modeling studies (Marr, 1970; Marr, 1971; Squire et al, 1984). This paper spurred interest into Marr's theories of hippocampal learning, especially pattern separation and completion; however, as discussed in *Studying episodic memory* animal work on episodic memory had been unsuccessful for various reasons, and many of these labs were now focused on research related to *Spatial navigation*, and moreover, there were not easily accessible methods to probe the activity of human hippocampus – intracranial studies were exceedingly rare and fMRI had only recently been developed in 1990 (Nobre et al., 1994; Ogawa et al., 1990; Wilson et al., 1990).

Eventually, the spatial navigation research actually served as a framework to show the first evidence for the existence of a pattern separation mechanism in the hippocampus, and in 2004, three papers were published showing suggestions of pattern separation in CA3 of rodents (Lee et al., 2004; S. Leutgeb et al., 2004; Vazdarjanova & Guzowski, 2004). All three studies used tasks in which rats were allowed to freely explore environments which parametrically varied from one another – e.g. shape of the room, orientation of room, or the placement of objects in the room – and the activity of purported place cells in CA1

and CA3 were analyzed in each environment – using electrophysiology in two studies and cellular analysis of temporal activity by fluorescence in-situ hybridization (catFISH) imaging of immediate early genes (Arc/H1a) in the other. Together, the studies showed that place cell representations in CA1 varied approximately linearly in response to changes in the environment, whereas the representations in CA3 were initially stable to small changes but exhibited a step like change to more significant changes. The non-linear response in CA3 was interpreted as evidence for a switch-like shift between pattern completion and pattern separation processes: when changes are small, CA3 pattern-completes – i.e. exhibits an overlapping representations of the environment, thereby facilitating the recognition of similarities – but when changes are large, CA3 pattern - separates – i.e. exhibits a non-overlapping representation (Guzowski et al., 2004). Follow up studies using a similar paradigm demonstrated that DG – which had already been shown to exhibit sparse coding (Jung et al., 1994)– featured a step-like response even to small changes in input, implying that DG has a bias toward pattern separation processes (J. K. Leutgeb et al., 2007; Sahay et al., 2011).

Soon after these rodent studies, pattern separation was investigated in humans, using the rapidly developing techniques of fMRI. The first study utilized an image recognition task: at encoding, a set of images were shown, and then at retrieval, a second set of images was shown comprised of a subset of the images from encoding (targets) and others that were similar to a subset of the items at encoding (lures). The study compared the activity in CA1 and CA3/DG (CA3/DG was grouped together due to limitations in MRI resolution), and showed that the BOLD response to targets in CA3/DG was reduced compared to the initial presentation at encoding, but the response to lures was comparable

to initial presentations; in contrast, the response in CA1 at retrieval was reduced relative to initial presentations for both stimuli. Because the BOLD response to lures in CA3/DG was comparable to BOLD response at encoding, this was interpreted as evidence for pattern separation: CA3/DG was responding to similar stimuli as if they were novel (Bakker et al., 2008). Follow up studies provided more comprehensive evidence of this using a variant of the previous task with lures of low and high similarity and foils (highly distinct pairs of images), providing four levels of parametric variation in stimuli, and showed input-output response profiles for CA1 and CA3/DG that were analogous to the rodent studies. As a final note, evidence of pattern separation has also been demonstrated in non-human primates with a similar image recognition task, but instead directly measure hippocampal electrophysiology (Sakon & Suzuki, 2019).

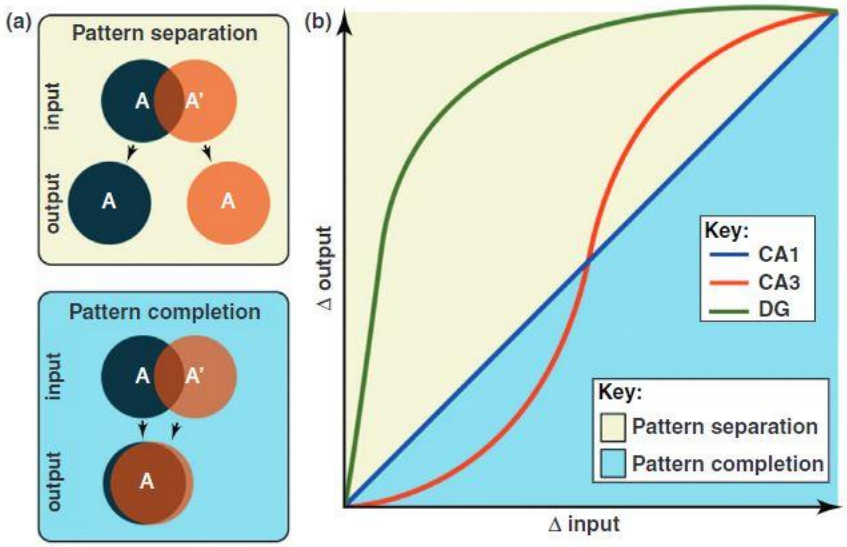

Figure 4: Pattern separation

(a) An illustration of pattern separation/completion (b) Summary of neural evidence for pattern separation in the hippocampus, from (Leal & Yassa, 2018)

Theta activity in episodic memory

Complex systems do not forget their history: they carry their history on their backs.
-Ily Prigogine-

Theta was first shown in rabbits spontaneously and in response to pain (Richard Jung et al., 1938). Several decades later, a study in rats linked this hippocampal rhythm to memory. It involved an inhibitory avoidance task in which rats were administered an aversive foot shock in a particular compartment of a cage and their memory of the compartment-shock association was assessed a couple days later by how long it took them to step back through the compartment; it was shown that the duration of theta following the initial foot shock training was highly correlated with the subsequent avoidance behavior (Landfield et al., 1972); it further showed that stimulation at (100 Hz ~ High gamma) and low (7 Hz ~ Theta) frequencies during the post-shock period improved memory (Landfield et al., 1973). However, as previously discussed, most studies on theta in animals are related to spatial navigation.

Non-invasive human EEG and MEG studies show theta activity positively correlates with successful memory, but interestingly, invasive intracranial studies, which can directly probe hippocampal activity, largely show either both increases and decreases, or exclusively decreases (Herweg et al., 2020). Theta has also been linked to plasticity, specifically stimulation or neuronal firing during the peak of theta oscillations indues long-term potentiation, but when occurring during the trough produces long-term depression (Huerta & Lisman, 1995; Hyman et al., 2003; McCartney et al., 2004; Pavlides et al., 1988)

Pre-stimulus theta activity in episodic memory

If the past is over, and the future has not yet come, all that exists is now; so how long does now last?
-St. Augustine-

Our mental state prior to encountering an experience, e.g., task directives, whether one is focused, stressed, anticipating a reward, etc., can affect how well we later remember it (Craik & Lockhart, 1972). Likewise, several studies have reported that brain activity prior to encountering a stimulus is related to successful encoding in fMRI (Adcock et al., 2006; Park & Rugg, 2010). Furthermore, such pre-stimulus activity has been shown in electrophysiology of humans (Dijk et al., 2008; Linkenkaer-Hansen et al., 2004; Mazaheri et al., 2009); and additionally, in animals (Griffin et al., 2004; Seager et al., 2002)

At least five human electrophysiology studies using variations of a word recognition task have reported increases in pre-stimulus theta activity associated with successful memory. In one study, intracranial EEG was acquired from the hippocampus, and a simple word recognition task was used to show that pre-stimulus theta in the hippocampus during encoding was greater for subsequently remembered words (Fell et al., 2011b). In three EEG studies, participants were asked to make a judgement about the words during encoding. In the first, subjects were asked to either rate the word's pleasantness (deep condition), or count its syllables (shallow condition) and in both situations, there was greater pre-stimulus theta activity during encoding for subsequently remembered words (Guderian et al., 2009). In the second study, subjects were asked to either rate the pleasantness of the word or the animacy of the object a word represents, and during recall subjects first responded to whether the word was new or old, and if it was old, they indicated which judgment they had previously had to make about the word (the source memory); this was

the only study that analyzed retrieval trials, and it showed a that pre-stimulus theta was only greater for recognized words if the source memory was also recalled (Addante et al., 2011). In the last study, subjects were asked to either rate the animacy of the object a word represents, or rate how useful the item would be for survival on a desert island, but in this study, the pre-stimulus encoding effect was only seen for the survival condition (Fellner et al., 2013). In the last EEG study, a value indicating a monetary reward for subsequent recognition preceded the word, and the power of pre-stimulus theta was correlated with the size of the reward (Gruber et al., 2013). Finally, this phenomenon has also been demonstrated in non-human primates (Macaca mulatta) engaged in a recognition memory task. For this task, each image of a set was shown to the subject twice, and the persistence of the monkey's gaze was operationally defined as recognition memory: if the monkey spent less time exploring the image on its second presentation, they "recognized" the image. In this study, pre-stimulus theta activity at encoding was associated with better recognition memory (Jutras et al., 2013). Together these studies suggest that pre-stimulus theta activity, improves subsequent recognition memory. A few tasks further suggest that this effect is modulated by task demand or incentivization. Although localization is poor for non-invasive studies, a single iEEG study in humans and another in monkeys implicate the hippocampus's involvement. Perhaps, this pre-stimulus theta activity represents a preparatory brain state, which facilitates the proximate encoding of the stimulus into episodic memory.

Pattern separation of emotionally arousing stimuli

"[m]emory is assisted by anything that makes an impression on a powerful passion, inspiring fear, for example or wonder, shame or joy"
-Francis Bacon-

The task used in this study is very similar to the task that was originally used to show evidence of pattern separation in humans: it involves three categories of stimuli based on how they are paired between the encoding and retrieval phases: (1) targets – pairs of the same image, (2) lures – pairs of similar images, or (3) foils – pairs of easily distinguishable images; however, there were also three emotional valences associated with stimuli either (1) negative, (2) positive, or (3) neutral (Lacy et al., 2011; Leal, Tighe, Jones, et al., 2014) This task has been used in the Yassa lab in combination with fMRI for various studies showing several interesting results such as differences related to age as well as depression and stress (Cunningham et al., 2018; Leal, Tighe, & Yassa, 2014; Leal, Tighe, Jones, et al., 2014; Leal et al., 2016, 2017a; Leal & Yassa, 2014). However, the most relevant results for the purpose of this dissertation were an increase in BOLD activity in CA3/DG for correct rejections vs false alarms to lure stimuli during retrieval; additionally, for correct rejections, BOLD activity in the hippocampus for negative items was greater than neutral items, and in the amygdala BOLD activity was greater for negative items regardless of whether they were subsequently remembered or not (Leal, Tighe, Jones, et al., 2014).

This task was also used by Zheng et. al. for an iEEG study in humans; in fact, this study analyzed the same dataset used in this dissertation (Zheng et al., 2019). Whereas this dissertation focuses on encoding, Zheng's study examined retrieval trials and investigated the relationship between theta and alpha rhythms in the hippocampus and amygdala. First, the authors showed that post-stimulus theta power was greater and alpha power was

reduced for lure correct rejections (LCR) vs lure false alarms (LFA). Additionally, they demonstrated that there was a bidirectional interaction between the hippocampus and amygdala in the theta range which modulated high gamma activity of the other region for LCR, but that during LFA there was a unidirectional interaction from the amygdala to the hippocampus in the alpha range which modulated the high gamma activity of the hippocampus. Like Leal's original study, many of the effects tended to be greatest for negative stimuli, potentially reflecting differences in emotional arousal (Leal, Tighe, Jones, et al., 2014; Zheng et al., 2019).

METHODS

Participants

All subjects in this study were recruited while undergoing treatment for medically-resistant epilepsy at the University of California, Irvine Medical Center. Intracranial depth electrodes (Integra or Ad-Tech, 5-mm inter-electrode spacing) were implanted stereotactically with robotic assistance (Rosa Surgical Robot, Medtech, New York, NY) for the sole purpose of informing medical treatment of these patients. Each subject provided informed, written consent to participate in the study as stipulated by the Institutional Review Board of the University of California Irvine. The task was administered by university researchers, and at the discretion of the subject and of their attending medical professionals. A total of 7 subjects were included in the study, 3 males and 4 females, ranging in age from 21 to 58 (*Table 1*).

Subject code	Age	Sex	Epilepsy	Dominant hand	Primary language	Other notes	# HPC Channels		
							Manual	Task active	Total
S1	21	Male	Right MTL – Left?	Right	English	Medicated	0	4	9
S2	40	Female	Right SMA	Left	English	Tired; line noise	9	7	9
S3	58	Female	Left HPC	Right	English	None	0	6	10
S4	32	Female	Right TL	Right	Vietnamese	Medicated tired and slow	5	3	11
S5	24	Male	Right MTL	Right	English	High IQ	16	10	16
S6	55	Female	Right MTL	Left	English	Happy	5	16	10
S7	23	Male	Right MTL	Right	English & Spanish	High IQ; good mood, but bored	0	0	11

Table 1: Subject information

Task

The task was a variant of the task originally used to study pattern separation in humans, but it was designed to probe the emotional modulation of memory, and likewise each image was associated with one of three emotional valences (negative, neutral, or positive) (Bakker et al., 2008; Lacy et al., 2011; Leal, Tighe, Jones, et al., 2014; Yassa et al., 2011). The task was created with PsychoPy2 (Version 1.82.01) software (Peirce, 2009) and was administered by a trained researcher while the subject was under passive medical observation (continuous iEEG, video monitoring, and vitals checked intermittently by a nurse) in a hospital bed. The subject completed the task using an Apple MacBook Pro positioned at a comfortable height and distance on an adjustable hospital table.

The task involved a training phase and testing phase. Each phase was preceded with written instructions on the screen which were read aloud and clarified, if necessary, by the researcher. Following these instructions, a set of images was shown in pseudo random order: First a black screen with a white fixation cross was displayed for 500ms; this was followed by an image displayed for 2000ms; the image was replaced with white text listing possible responses and a corresponding number; finally, the subject was given up to 2000ms to respond by pressing a number key on the keyboard to indicate their choice. This presentation sequence continued until that phase of the task was complete (see *Figure 5*, used with permission from (Zheng et al., 2019)).

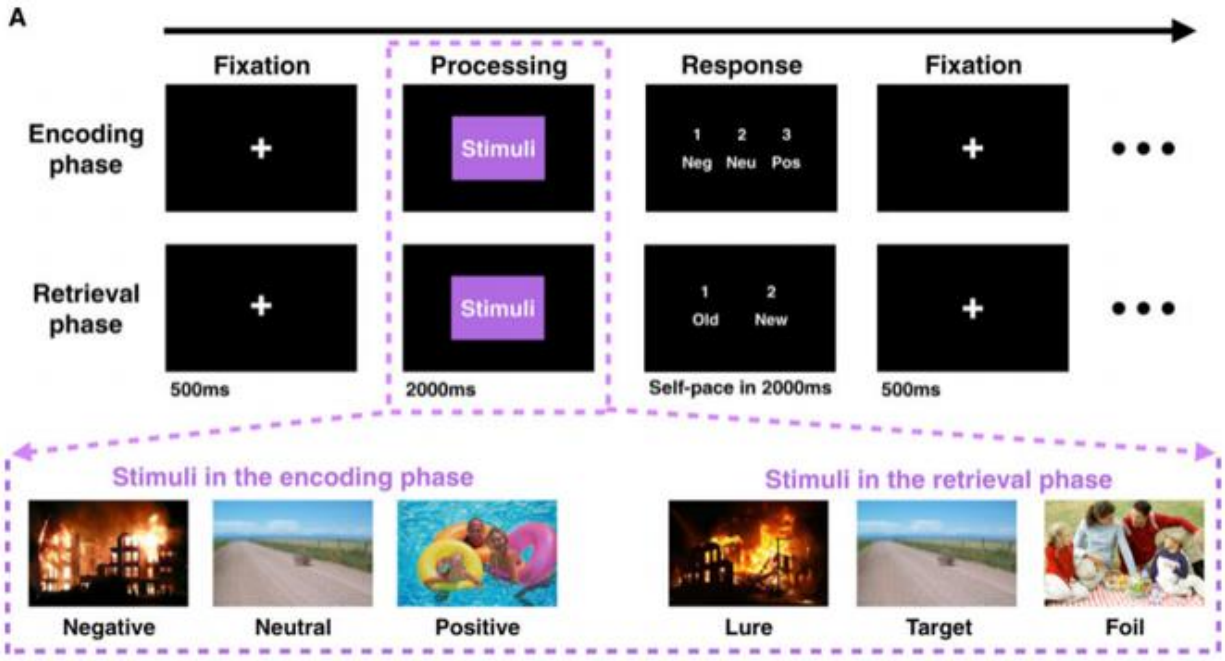

Figure 5 Task design

From (Zheng et al., 2019)

During the training phase, subjects were shown a set of 148 images and asked to classify the emotional valence of each image (negative, neutral, or positive). Following this phase, subjects were given the option to take a short break before beginning the test phase. During the test phase, subjects were shown a set of 290 images composed of targets (exact repeats from the training phase n = 54), foils (new images n = 139), and lures (new images, which are similar to one previously shown in the training set n = 97); lure items were evenly distributed across emotional valence (Negative = 33; Neutral = 32; Positive = 32) and (similarity level (NegSIM = 6.29 ± 0.11; NeuSIM = 6.14 ± 0.12; PosSIM = 6.41 ± 0.08, $p > 0.05$) (Zheng et al., 2019). Following each image presentation, subjects were asked to respond with a keystroke indicating whether it is old (previously shown during the training phase) or new. In the case that no emotional choice was made in the allotted 2s during the training phase, the stimulus was designated as the independently rated

emotional type (see “Stimuli” below); however, if no response was made during the testing phase, the corresponding training trial was removed from analysis.

Stimuli

The stimulus set was freely acquired online and consisted of various scenes. In a prior, independent experiment, a group of undergraduates (N= 50, 32 female, age 22 ± 5) rated each image on the basis of emotional. In a second experiment (N = 31, 21 female, age 19 ± 1), similarity was rated for lure stimuli pairs on a scale of 1 to 8, with 1 indicating distinct that image pairs were distinct and 8 indicating images were identical. In a third study (N= 16, 4 female, age 23 ± 5), stimuli were rated for emotional arousal on a scale of 1 to 9 – 1 indicating it was not arousing and 9 indicating it was highly arousing. Negative stimuli were collectively the most arousing and neutral stimuli were the least arousing category. While each emotional valence was represented almost equally in the stimulus set and lure similarity was balanced across valence, arousal is a very difficult feature to balance across valence, and unfortunately, arousal also influences memory and brain activity in the MTH; this will be discussed further in the Results and Discussion sections (Fastenrath et al., 2014; Madan et al., 2017; Mather et al., 2006; Packard & Goodman, 2012). For additional details on these supplementary studies, see the original paper (Leal, Tighe, & Yassa, 2014).

Another potential issue is that content within an emotional valence tends to relate thematically relative to neutral content, which could lead subjects to perceive that emotional lures are relatively more similar than neutral lures (Talmi & Moscovitch, 2004). So, another independent study was designed to assess similarity between pairs across

valence and trial type (27 participants, 11 females; via Amazon Mechanical Turk), and confirmed this effect would not confound our results (no significant difference across valence: $Similarity_{negative} = 5.47 \pm 0.13$, $Similarity_{positive} = 5.39 \pm 0.11$, $Similarity_{neutral} = 5.64 \pm 0.14$, $p > 0.05$; no significant difference across trial type ($Similarity_{target} = 5.68 \pm 0.12$, $Similarity_{lure} = 6.21 \pm 0.28$, $p > 0.05$; and no significant interaction: $p_{valence \times trial\ type} > 0.05$). For additional information on this supplementary study, see the original paper (Zheng et al., 2019).

Finally, the visual characteristics of an image can affect how it is processed, so using the same methods published with the "Nencki dataset" (Marchewka et al., 2013), the images used in our study were balanced for size, luminance, brightness, contrast, complexity, color composition, and color tone across each valence. Additionally, brightness and color tone were assessed for image pairs subjectively by an independent group (11 participants, 4 females), confirming that visual features of the images were roughly balanced across valence (brightness t-test: $p = 0.187$; color tone: subjects rated stimulus pairs as balanced for 82.2, 91.1, and 94.2% for negative, positive, and neutral images pairs). For additional information on this supplementary study, see the original paper (Zheng et al., 2019).

Electrode localization

Electrodes were localized to brain anatomy with a pre-implantation T1-weighted MRI, which has great soft-tissue contrast, and a post-implantation CT, which is sensitive to differences in material density. First, each subjects' volumetric imaging was co-registered, i.e., the subjects' post-implantation CT was transformed into the space of the pre-

implantation T1-weighted MRI, using a six-parameter rigid-body transform. Each electrode, appearing as a bright spot in the post-implantation CT volume, was manually segmented with a MATLAB GUI and transformed into MRI coordinates (Stolk et al., 2018). The coordinates of the segmented electrodes were then localized to the anatomical region in which it laid manually and automatically. Manually, localizations were based on expert interpretation of the MRI with the coordinates of electrodes superimposed. This was performed independently by three laboratories. Notably, one laboratory's localization involved an additional coregistration step that transformed the subject's MRI to a high-resolution MRI template with hippocampal sub-fields for more accurate localization (Zheng et al., 2019). Automatic localization was performed by matching the electrode coordinates to a several automatic brain parcellations (recon-all from FreeSurfer) (Dale et al., 1999; Desikan et al., 2006; Fischl et al., 2002). If electrodes were not unanimously labeled among experts from all three labs, a consensus was determined which also considered various automatic localizations. Note that subject IR44, only had post-implantation CT scans, all localizations were performed by manual localization of experts.

Data acquisition and preprocessing

Intracranial EEG (iEEG) data were acquired with a Nihon Kohden recording system (256 channel amplifier, model JE120A, highpass; analog filtered at 0.01Hz and sampled digitally at 5000Hz) while subjects were engaged in the task on an Apple Macbook Pro. Keystrokes from subjects' responses during task were logged with the PsychoPy2 (Version 1.82.01) software (Peirce, 2009). Time-stamps were logged for each response with a keystroke latency ~4-25ms. To attain accurate stimulus onset/offset times, a small portion

of the screen (~ 1x2 in) at the bottom left of the monitor was programmed to illuminate black as a fixation cross or text was presented and white as stimuli were presented; a photodiode was attached to this portion of the screen, completely obscuring its illumination, and the signal from this sensor was acquired through the same Nihon Kohden recording system acquiring iEEG, thus ensuring accurate time alignment.

The resulting datasets are on the order of gigabytes due to the number of channels recorded and the high sampling rate. To reduce the size of the dataset and because our hypotheses about memory encoding involved the hippocampus, only hippocampal channels were analyzed. Furthermore, data processing methods like time-frequency decomposition increase the size of data exponentially, so to reduce computational burden, data were down-sampled via interpolation with an antialiasing finite impulse response lowpass filter from 5000Hz to a lower rate (resample.m, in Signal Processing Toolbox from MATLAB) for each analysis.

Voltage, or electrical potential difference, is the difference in electrical potential energy between two points and is caused by the charge imbalance between the two places, e.g., differences in concentration of ion species between locations in the brain. The Nihon Kohden recording system has a ground electrode, to which all recording electrodes are referenced, but there is inevitably electrical noise present in this ground due to interference between circuits of the recording system and the various external sources in the environment, e.g., lighting, health monitors, hospital bed, etc.; furthermore, neuroscientists wish to assess how brain signals vary throughout the brain. Re-referencing EEG signals from the ground electrode to some other electrode in the recording array – via simple subtraction – eliminates the common electrical noise in the ground and diminishes

noise localized to the electrode array, thus providing a better basis in which to compare brain signals. Choice of reference is a controversial topic with good arguments supporting various choices, but the consensus is that the appropriate choice depends on the specific analysis. I wrote code to flexibly switch between bipolar (adjacent electrodes), full electrode array average, probe-wise average, and other referencing schemes, but reference was found to have only a modest effect on time-frequency decomposition. Ultimately, a bipolar montage was used for all analyses because it is the most common scheme in the iEEG literature and emphasizes local differences between channels.

All patients in this study had medically resistant epilepsy at the time of the experiments, and a hallmark feature of an epileptic brain is aberrant brain electrophysiology known as epileptiform activity. For clinical purposes, there is a thorough taxonomy of the various types, but most often it is manifested as sharp, high amplitude transients often followed by low frequency activity called interictal epileptiform discharges (IEDs). The high amplitude can endure up to a second and its spike-like morphology causes this increase in power to be spread broadly across frequencies. Because of the sporadic occurrence and broadband power increase, these artifacts are much more detrimental than electrical noise which is more persistent, but well isolated in frequency to harmonics of 60 Hz. I tried three methods to mitigate spurious results due to epileptiform activity. First, raw iEEG trial data was visually inspected and marked by a trained epileptologist to be removed (J.J. Lin) (Zheng et al., 2019). Second, I wrote a simple automatic detection algorithm: briefly, montage-averaged power was computed for each trial and z-scored over all trial data; if the maximum power during the trial was greater than a particular threshold, the trial was removed. Finally, trial averaged data was visually inspected from

each hippocampal channel after removing putative artifactual trials using one of the other two methods, and if broadband artifacts were noted in the trial averaged data, the electrode was discarded from analysis.

Task active electrodes

To further reduce the size of the dataset, and increase signal to noise, I only used a subset of hippocampal electrodes that were determined to be task responsive. To this end, each trials was divided into five 500ms windows, one before and four following stimulus onset. The fast Fourier transform was computed on each window, and total power for the window was calculated as the summation of power over all frequencies. I then tested whether there was a statistically significant difference in power between these windows over all trials, irrespective of trial type with (ANOVA, $p<.01$, Bonferoni corrected).

Morlet wavelet convolution

Time-frequency power was computed via Morlet (Gabor) wavelet convolution. Essentially, Morlet wavelets are short oscillations (complex exponentials) weighted by a Gaussian.

$\boldsymbol{w = e^{2i\pi ft} e^{\frac{-4\ln(2)t^2}{h^2}}}$, where f, t, and h are time, frequency, and the FWHM, respectively. The complex exponential determines the center frequency of the wavelet, while the Gaussian term defines the extent of temporal averaging, thus establishing the trade-off between time and frequency resolution (see *Figure 6*). The uncertainty principle, also known as the Gabor limit in signal processing, states that a signal cannot simultaneously be localized in the time and frequency domain.

$\boldsymbol{\sigma_t \cdot \sigma_f \geq \frac{1}{4\pi}}$, where σ_t & σ_f are standard deviation for time and frequency, respectively.

Data was first epoched by trials in a 2.5s window spanning 500ms before and 2000ms after stimulus onset with an additional 500ms of data padding on either side to prevent edge effects in the low frequency bands; trials were then concatenated; the FFT was computed for both the concatenated data and wavelets; these spectra were multiplied to compute the wavelet convolution spectrogram; the time-frequency data was de-concatenated; additional trial padding was removed; the analytic amplitude was isolated and squared to compute power; and finally, these data were z-score normalized within each frequency band using the mean and standard deviation derived from all trial data.

The parameters of the wavelet convolution were set to optimize resolution for the power spectral density of EEG, which has been characterized as a power-law and collection of intermittent oscillators with center frequencies approximately in multiples of *e* (Buzsáki & Draguhn, 2004). Frequencies were spaced geometrically in multiples of $\frac{e}{N}$ between 0.8 – 1000 Hz (see *Figure 6*). The lowest and highest frequencies were chosen heuristically, as the lowest frequency for which 2 cycles could be fully represented in the trial window ($\frac{2\ cycles}{2.5s} = 0.8Hz$), and the highest frequency as a number below the Nyquist frequency above which is unlikely to be related to neural activity (1000Hz).

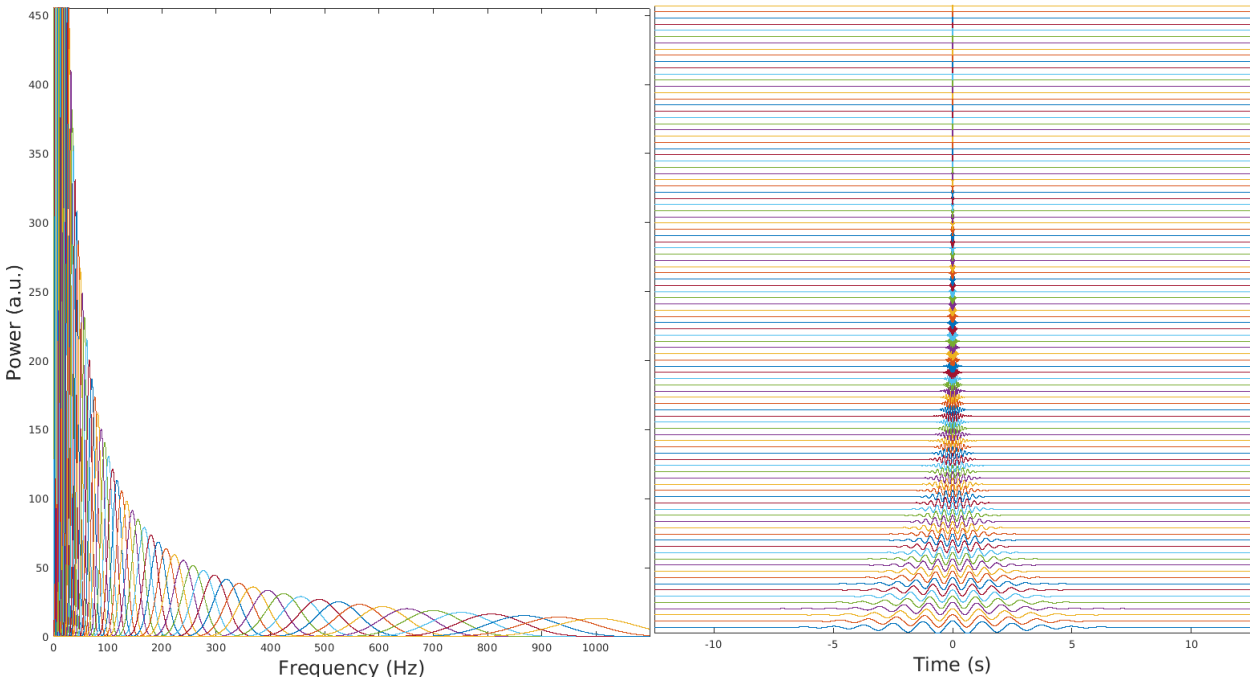

Figure 6: Wavelet frequency and time resolution trade-off

A subset of the wavelets used to derive trial spectrograms to the illustrate the frequency (left) and time resolution (right) trade-off.

Finally, these conditions were compared statistically using permutation testing with cluster-based correction (Function ft_timelockstatistics from Fieldtrip toolbox, 2000 permutations, $p<.05$). Specifically, for every time-frequency data point, the LCR vs LFA power distributions were compared via two-tailed t-test; if a time-frequency data point had a significant conditional difference, it was clustered with the significant time-frequency data points adjacent to it; these empirical clusters were then compared to a Monte Carlo distribution created by shuffling trial labels and computing t-values for the same time-frequency region defined by the cluster 500 times; finally, a conditional difference in power was deemed significant if the summed t-values for an empirical cluster exceeded a the 95th percentile of the Monte Carlo distribution.

Bandpass filtering

Additionally, power differences were assessed by bandpass filtering data into canonical bands (low-frequency activity: .08-1Hz; delta: 1-3Hz; theta: 3-8Hz; alpha: 8-15Hz; beta: 13-30Hz; gamma: 30-55Hz; high-gamma [HG]: 65-115Hz; higher-gamma [HHG]: 125-250Hz; high frequency activity [HFA]: >250Hz). Similar to the method described above for wavelet convolution, each trial was segmented, padded, concatenated, then finite impulse response bandpass filtered, de-concatenated, de-padded, and Hilbert transformed (bpfilter.m and hilbert.m from Signal Processing Toolbox in MATLAB). For the power analyses, the analytic amplitude was squared and z-score normalized within each band using the standard deviation and the mean derived from all trial data.

Conditional differences (LCR vs LFA) were assessed independently for each emotional valence using permutation cluster-based correction (as described in *Morlet wavelet convolution* above). Additionally, power differences were assessed in windows, and compared via T-test.

RESULTS

All enquiry and all learning is but recollection.
-Socrates (in Plato's Meno)-

Task performance

Seven epilepsy subjects implanted with intracranial EEG took part in this study (3 males and 4 females) (*Table 1*). Task performance by subject is summarized in *Table 2*. In order to measure how well participants discriminated similar items (lures), task performance was previously quantified by Zheng et. al. (2019) using a bias-corrected LDI operationalized as p('New'|Lure) – p('New'|Target) (Yassa & Stark, 2011; Zheng et al., 2019). Recapitulating similar studies, the LDI for emotional stimuli is diminished relative to neutral items (Fvalence × LDI (subject number × 3)(2,18) = 6.32, p = 0.008) (post hoc analysis, Scheffé test: d|Neg − Neu| = 0.272, CV |Neg − Neu| = 0.219, p < 0.01; d|POS − Neu| = 0.171, CV|POS − Neu| = 0.169, p < 0.05, where Neg, negative; Neu, neutral; and Pos, positive) (Leal, Tighe, & Yassa, 2014; Leal, Tighe, Jones, et al., 2014; Leal & Yassa, 2014; Zheng et al., 2019). Note that the effect was greater for negative stimuli than positive stimuli, which could be related to the fact that greater arousal is elicited by the negative condition (Lang et al., 1993). Only subjects with an overall discrimination accuracy greater than 65% were included in the study (79.8% ± 1.8% accuracy, mean ± SEM; range = 73.1%–86.6%, Table 2; chance level = 54.8%, p < 0.05, permutation test).

Subject code	No response	Mean RT (s)	Target hits (%)	Lure hits (%)	Foil hits (%)	LDI (%)
S1	13	2.971	100.0%	67.0%	91.4%	67.0%
S2	2	2.585	100.0%	61.2%	83.2%	61.2%
S3	1	2.596	95.8%	72.0%	93.7%	67.8%
S4	116	3.085	97.5%	71.8%	64.4%	69.3%
S5	3	2.603	95.9%	60.2%	96.5%	56.1%
S6	3	2.542	98.0%	64.6%	81.0%	62.6%
S7	10	2.608	100.0%	60.0%	91.3%	60.0%

Table 2: Subject performance

Time-frequency response at encoding

Extracellular potentials were recorded in the hippocampi of 7 pre-surgical epilepsy with stereotaxically-implanted depth electrodes during the administration of the EmoPS task. The objective of this study was to assess whether hippocampal activity during encoding contains a signal related to subsequent memory performance. Likewise, the analysis was restricted to channels localized to hippocampus and only encoding trials were analyzed.

To determine which electrodes were recording from the hippocampus, the subjects' volumetric imaging was co-registered, i.e., the subjects' post-implantation CT was transformed into the space of the pre-implantation T1-weighted MRI, such that the patients head anatomy optimally superimposed. Each electrode, appearing as a bright spot in the post-implantation CT volume, was manually segmented with a MATLAB GUI (Stolk et al., 2018). The coordinates of the segmented electrodes were then localized to the anatomical region in which it laid using the superior soft-tissue resolution of the MRI automatically and manually. First, electrodes were automatically localized according to where the electrode coordinates laid in each of several automatic brain parcellations (recon-all from FreeSurfer) (Dale et al., 1999; Desikan et al., 2006; Fischl et al., 2002), and additionally, (2)

based on interpretation of the MRI and overlaid electrode coordinates by experts from three laboratories. If electrodes were not unanimously labeled among the experts, a consensus was determined which also considered the automatic localizations.

Only encoding trials for which the subject responded to the corresponding retrieval trial, i.e., rating the paired retrieval stimulus as new or old, were analyzed. Trials were also grouped by the emotional valence of the stimulus (negative, neutral, or positive): if the subject labeled the emotional valence of the stimulus during the encoding trial, their own subjective valence rating was used, if not, the trial was assigned the standard valence label – derived as the consensus rating from subjects (11 subjects, 4 female) in an independent study administered on Amazon's Mechanical Turk (Zheng et al., 2019).

Hippocampal activity during the incidental encoding phase of the task was first visualized with spectrograms derived from *Morlet wavelet convolution* (varying the time-frequency resolution as a function of frequency - see *Methods*), and trial-epoched in a 2500 ms window – 500ms pre-stimulus and 2000ms post-stimulus (see *Figure 7*). To improve visualization of power over frequencies and facilitate comparisons across channels and subjects, each channel's power was z-scored within each frequency band using the mean and standard deviation computed across all timepoints in the analysis.

The stimulus-locked hippocampal response can be characterized roughly into three main bands: (1) low-frequencies (<2Hz), (2) mid-frequencies (4-25 Hz), and (3) high-frequencies (>35Hz) (see Figure 7, Figure 8). Prior to the stimulus onset, power is relatively low in the low- and high-frequencies, while power in the mid frequencies is high. About 100ms after stimulus onset, there is an evoked response in which low-frequency activity peaks while mid-frequency activity persists. At around 300ms, activity in low and

mid-frequencies coalesce to form a band around 1-3 Hz (canonical delta); coincidentally, high frequency power emerges at this moment. The high frequency power is initially more prominent in the high gamma band (50-150 Hz), then between 600-900ms the power between 50-300 Hz peaks, followed closely by an increase in low-gamma (35-50 Hz) around 700-1000ms. After about 1000ms, the high-frequency response gradually attenuates, but the power remains above pre-stimulus levels until the end of the trial window. Meanwhile, the mid- and low-frequency activity is largely absent from 400-1500ms, with the exception of the previously mentioned delta activity, which after 600ms shifts slightly higher to 3-4 Hz (low theta range) and persists at an attenuated level. Finally, around 1500ms, power in the low- and mid-frequencies increases to an intermediate level.

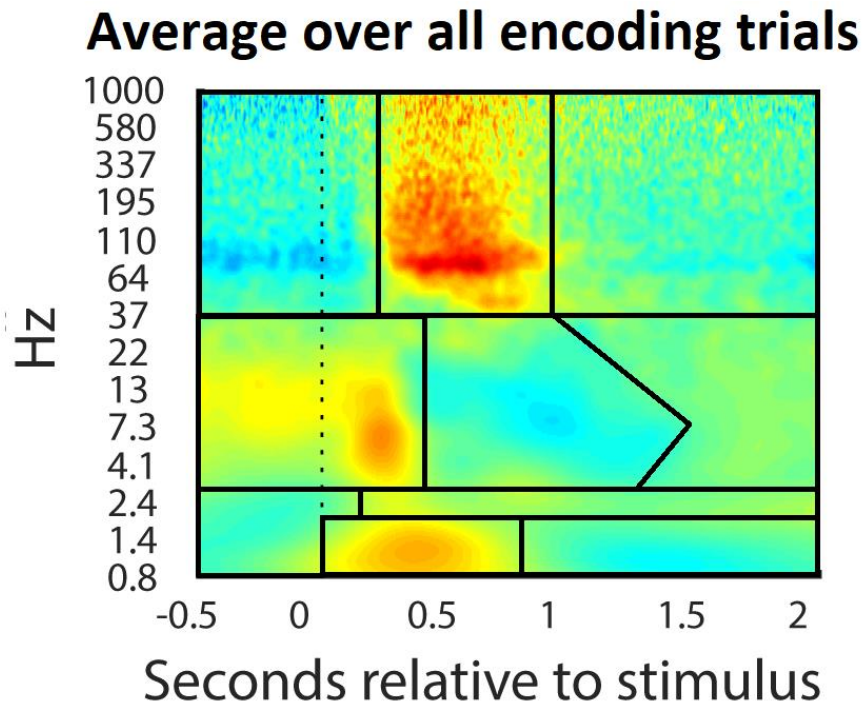

Figure 7: Stimulus locked time-frequency response.

Stimulus locked time-frequency response during encoding trials, averaged over all trials. Time-frequency windows of interest outlined in the all-trial average to better illustrate the stereotyped response.

Furthermore, in many of the time-frequency windows discussed above, power varies by emotion (*Figure 8*). For the majority of these windows, power was most extreme (highest or lowest) for the negative stimuli, and often intermediate for neutral, and least extreme for positive. Importantly, this pattern echoes the differences in arousal for valence types mentioned in *Stimuli*, implying these differences for emotional valence, might actually be driven by arousal. While this could have consequences for subsequent results, arousal values for the stimuli (as determined in the independent study) were not available, so the effect of arousal could not be evaluated (Leal, Tighe, & Yassa, 2014).

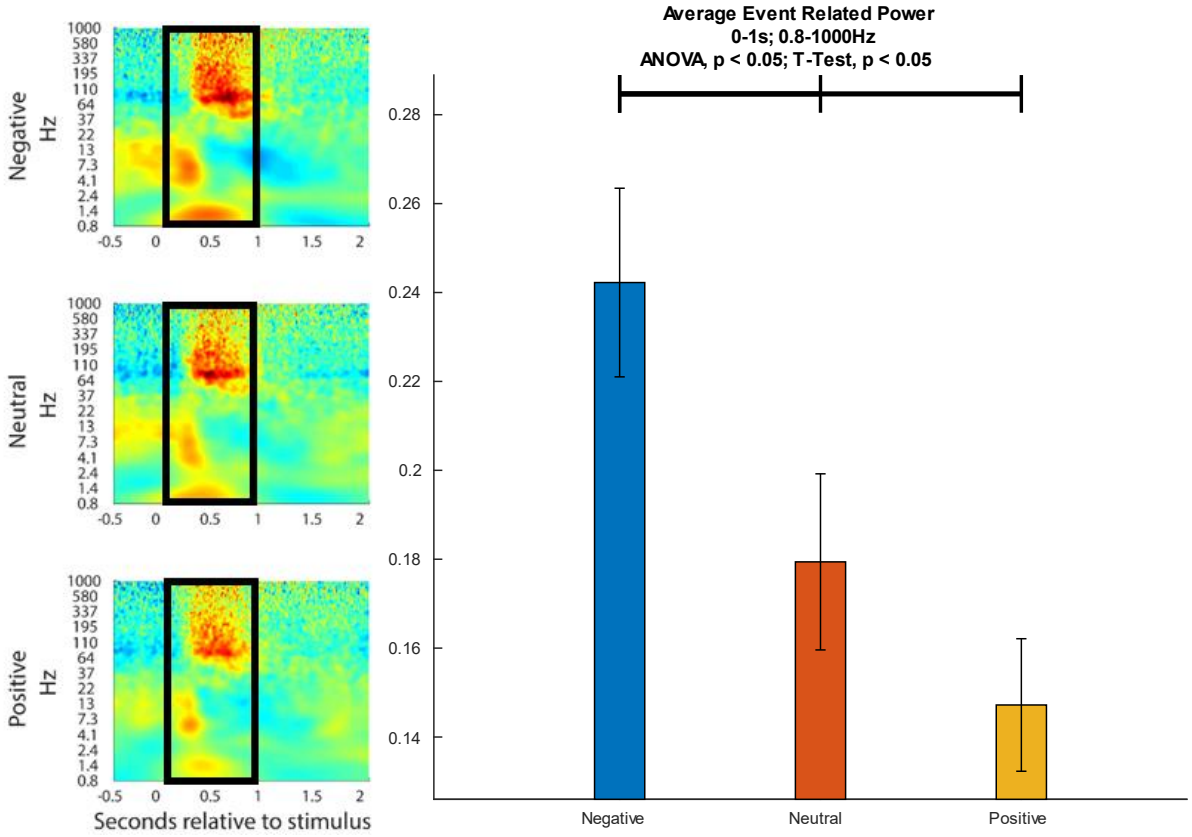

Figure 8: Power of stereotypical response varies by emotion.

Pre- & post-stimulus θ power are associated with LFA & LCR, respectively

To examine the relationship between time-frequency power and memory, trials were grouped into conditions by subsequent discrimination performance – i.e., whether, at retrieval, the subject rated the corresponding lure item as new (correct rejection – CR) or old (false alarm – FA) – and emotion, then compared (*Figure 9*). For each channel, spectrograms were averaged for LCR and LFA within each emotional category (positive, negative, neutral, and all), and the conditional differences in time-frequency response were assessed with a cluster-based permutation test. Briefly, t-values were computed quantifying the conditional difference in power (LCR-LFA) over channels at each time-frequency coordinate of the spectrogram, and contiguous bins with t-values above/below a threshold ($p<.05$) were identified as clusters; conditional labels were then randomly permuted and t-values within each of the identified clusters were calculated for this surrogate data; finally, if the summed t-values for the original cluster exceeded the 95^{th} percentile of summed t-values in the permuted data. This analysis revealed that pre-stimulus theta activity was lower for LCR relative to LFA, while post-stimulus (.5 to 1.5s) theta was higher.

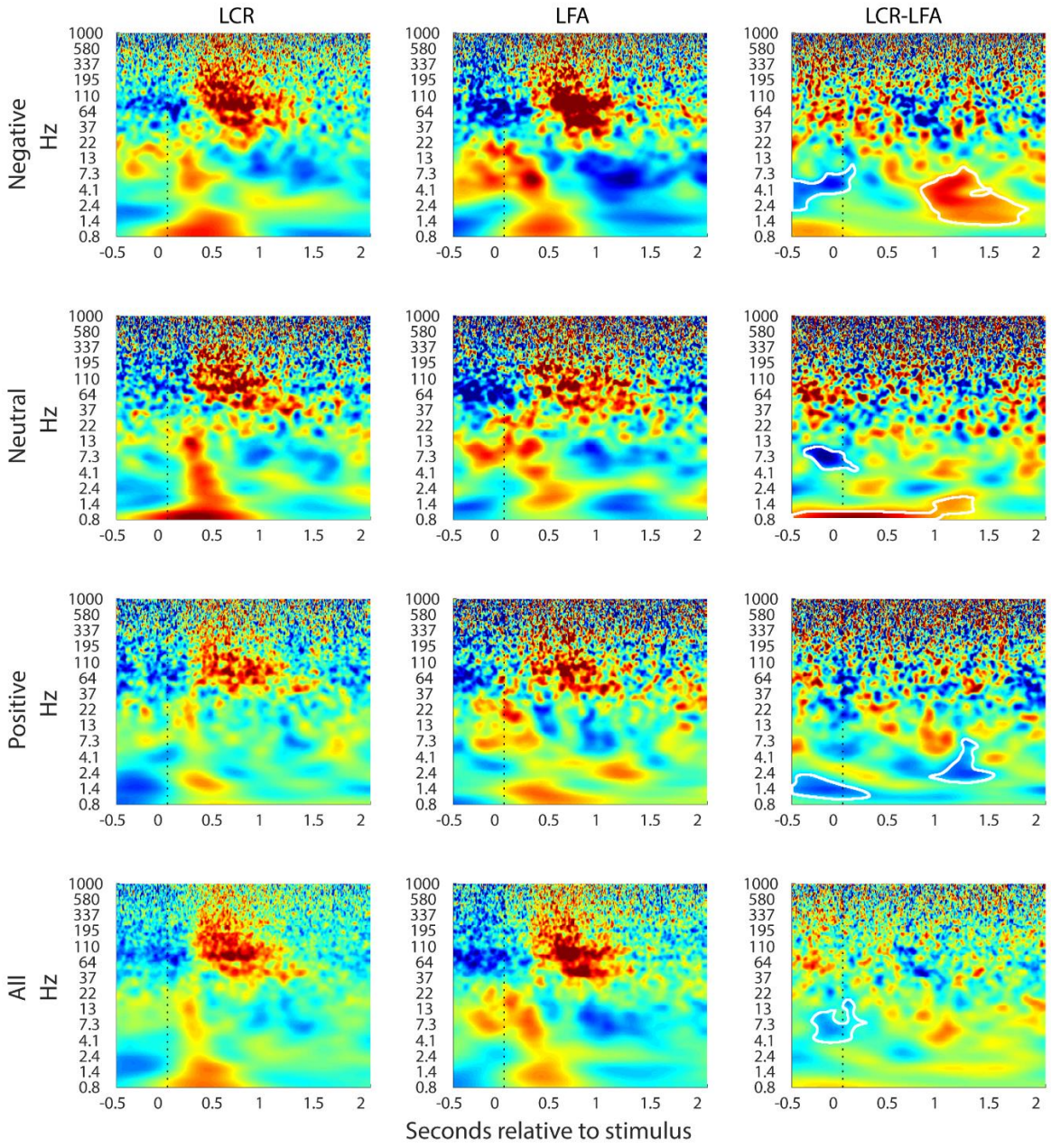

Figure 9: Conditional differences in wavelet spectrograms

A complementary analysis was done using band-pass filtering within canonically defined brain rhythm frequency bands (*Figure 10*). Notably, band-pass filtering provided an alternative method of time-frequency decomposition using a well-validated code (bpfilter.m in MATLAB) to corroborate results of my custom-built wavelet function, and moreover, using canonical brain rhythms facilitates the interpretation of results in the

context of the literature. The data was band-pass filtered between 3-8 Hz and the result was Hilbert-transformed to derive the instantaneous envelope and phase in this band. I first assessed conditional power differences over the duration of the theta time-series with a permutation test. Furthermore, theta power was averaged within pre-stimulus [-.5-0s] and post-stimulus [.5-1.5s] time windows and compared with a simple t-test (Figure 11).

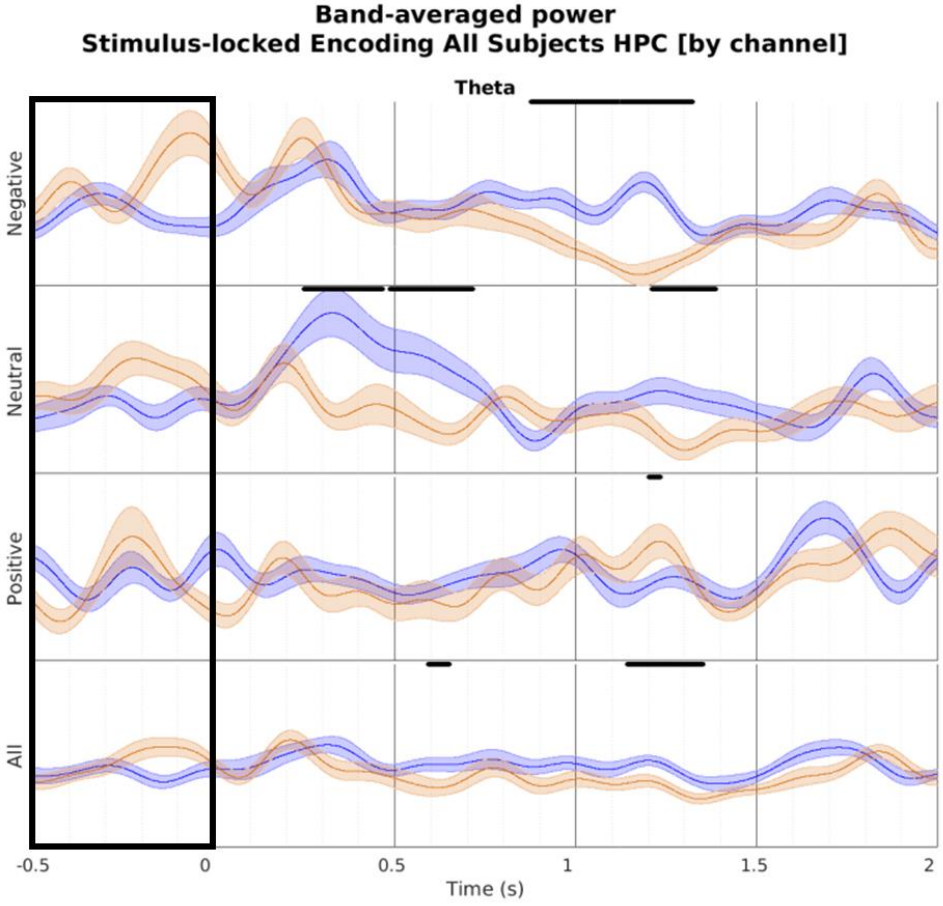

Figure 10: Conditional differences in band-pass filtered theta activity

[Legend: Blue = LCR, Orange = LFA].

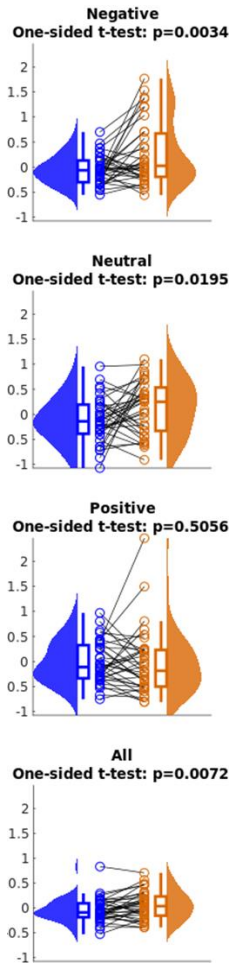

Figure 11: Raincloud plots of band-passed pre-stimulus theta power.

Raincloud plots show histogram and individual channel average theta power for each condition and during the pre-stimulus period [-.5 – 0s]. This analysis corroborates that pre-stimulus theta power is greater for LFA over all conditions, and particularly driven by negative stimuli. [Legend: Blue = LCR, Orange = LFA]

Other iEEG studies of the human hippocampus have not consistently documented this positive association of post-stimulus theta power with memory, and in fact, they tend to report the opposite effect; however, post-stimulus theta has been correlated to memory for most hippocampal studies in animals and in non-invasive human studies, and theta activity is an integral part of most theories about hippocampal memory function. It has been argued that these contradictory iEEG results may be confounded by methodological issues (Herweg et al., 2020). More curiously, the direction of this pre-stimulus effect ran contrary to previous accounts of pre-stimulus theta effects on memory (Addante et al.,

2011; Fell et al., 2011a; Fellner et al., 2013; Gruber et al., 2013; Guderian et al., 2009; Jutras et al., 2013). Both inconsistencies with the literature will be discussed further in the Summary and Conclusions section.

Post-stimulus high gamma activity is associated with lure false alarm

High frequency power in the spectrograms also appeared to be conditionally related (*Figure 9*), but it was not considered significantly different based on permutation tests. Critically, the permutation testing method used depends on identifying clusters of contiguous time-frequency bins beyond a defined statistical threshold. However, such a clustering approach might not be appropriate for high frequency activity because power in these frequencies tends to present as short, sporadic bursts, and the wavelet parameterization used endows high frequencies with very sharp time-resolution; although the frequency resolution is quite coarse, the electrical noise present at harmonics of 60 Hz introduce a spectral discontinuity, further confounding the formation of clusters. Therefore, a supplementary window averaged analysis was performed to reveal that high gamma activity is indeed lower for LCR relative to LFA.

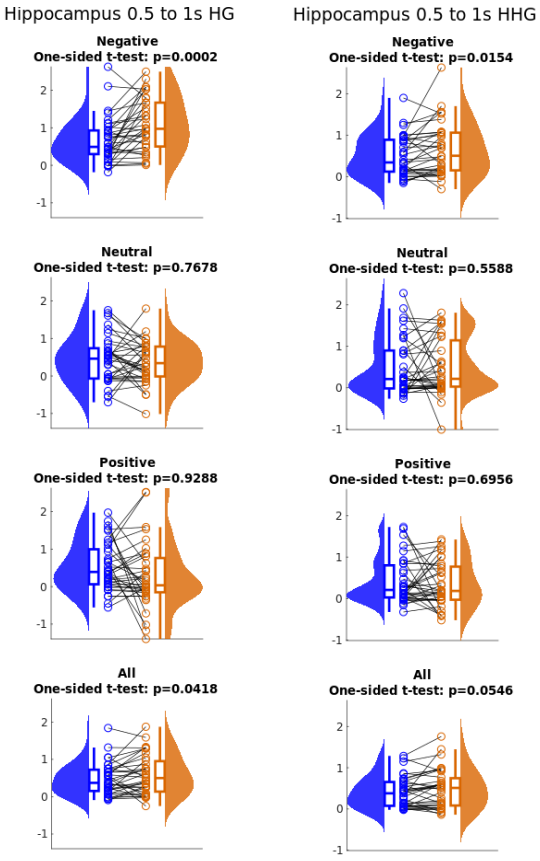

Figure 12 Conditional difference in high frequency activity

[Legend: Blue = LCR, Orange = LFA]

Correction for log-log slope

As discussed before, the power spectral density of EEG has the appearance of a power-law because there is an inverse linear relationship between log(power) and log(frequency). In addition to this slope, there are peaks in the power distribution, indicative of oscillatory activity. Importantly, this slope can change over the course of a trial or the duration of the task,

To control for this "1/f" EEG phenomenon, the log-log slope was subtracted from the wavelet derived spectrum at each time point before z-score normalization, and then LCR and LFA trials were compared as before. This analysis corroborated the results from the

uncorrected spectrogram (Figure 9). The new clusters corresponding to those from the previous analysis were larger and more irregularly shaped, and moreover, additional clusters were recovered (*Figure 13*).

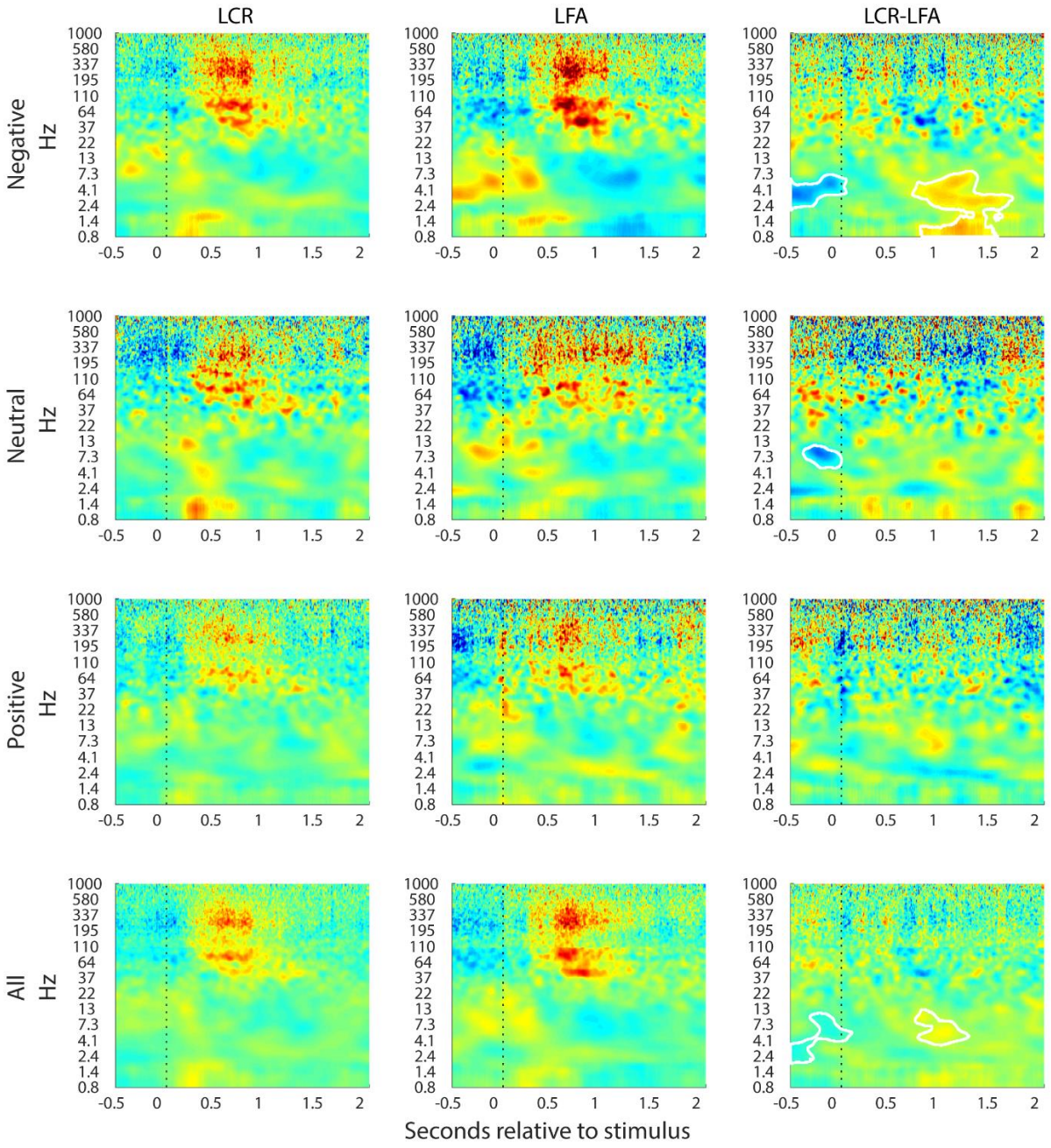

Figure 13: Conditional differences in wavelet spectrograms with "1/f" correction

SUMMARY AND CONCLUSIONS

If the brain were simple enough to understand it, we would be too simple to understand it.
-Ken Hill-

The study of the neurobiology of learning and memory is a product of its history, from the early introspection of philosophers attempting to better articulate what is the mind to computational models of memory, and from the crude mutilation of animal brains to the demonstration that harmonious patterns of hippocampal electrophysiology represent relationships between the subject and its environment in navigation and memory. Cognitive neuroscientists are tasked with formalizing imprecise descriptions of psychological phenomena into cognitive models, establishing a behavioral paradigm to derive suitable operational definitions of these constructs, selecting an appropriate model organism, and choosing ethical methods to measure the organism's behavior and brain at sufficient resolution to ultimately learn how psychology relates to brain processes. I began this dissertation by reviewing the relatively short and recent history of this field to illustrate how our scientific understanding about memory, the brain, and the relationship between them has grown quickly, but also to emphasize how imperfect this understanding is and how tortuous the path has been to reach the question I addressed in this dissertation: "is hippocampal electrophysiology – particularly the theta rhythm – at encoding predictive of subsequent recall?"

To answer this question, I analyzed intracranial EEG recordings from human hippocampus in subjects participating in an image recognition task. These subjects are epileptic and their brains features prominent epileptiform activity, which can confound analysis, so these artifacts were painstakingly addressed in several ways. However, when

the patients are not actively seizing, their cognition is typically normal and aberrant activity is primarily localized to their individual seizure onset zone; furthermore, decades of profitable research on cognitive neuroscience in epileptic patients and other clinical populations have produced results that are largely consistent with studies in animals without disease as well as non-invasive studies of healthy human subjects. So, while their epilepsy should not be ignored, and artifacts must be addressed in such studies, it is unlikely that our results were driven by their disease.

The results of this study offer evidence that post-stimulus theta is related to subsequent correct rejection of lure stimuli, while pre-stimulus theta activity is associated with subsequent false alarms. Both results have some inconsistencies with the existing literature.

First, post-stimulus theta has been extensively linked to navigation and spatial memory processes in rodents. With the growing support for the hypothesis that episodic memory emerged through evolution out of mechanisms in the MTH supporting navigation, this would suggest that hippocampal theta should likewise be related to episodic memory processes. While results from most non-invasive human studies do support theta's relationship with memory, the recording modalities are insufficient to implicate the hippocampus. In contrast, iEEG studies with depth electrodes record directly from the human hippocampus; however, the majority of these studies have reported either an inverse relationship between theta and memory performance or both negative and positive relationships.

This inconsistency was the topic of a recent review paper, which argued in favor of the hypothesis that theta is positively correlated with memory and offered several

explanations for why this was not apparent in iEEG studies (Herweg et al., 2020). First, the authors point out that the majority of these studies used a simple contrast of subsequent memory performance, i.e. subsequent correct vs incorrect recall, which can be confounded by neurocognitive processes unrelated to memory, e.g. task engagement and attention. However, all studies that made comparisons based on the degree of association among successful memories (associative memory contrasts), e.g., comparing correct recall trials with high confidence vs moderate or low confidence, reported that theta was positively correlated with the strength of memory association. These associative memory contrasts are thought to be superior because they are less susceptible to effects from non-mnemonic processes.

A second issue pointed out is that very few studies control for spectral tilt, i.e., changes in 1/f slope; as discussed above. This is important because it is possible for a power spectrum with an oscillatory peak at theta to have less theta power than a spectrum with no peak at theta if the slope of the latter is sufficiently steep. Taking this into consideration, it is possible that the theta rhythm was indeed present in the studies that demonstrated inverse relationships between theta and memory, but without controlling for spectral tilt these oscillations were drowned out in the average by broadband shifts in power.

The results of this study agree with the above perspective on hippocampal theta's role in memory. In line with the authors' suggestions, I controlled for spectral tilt, which indeed emphasizes narrow band differences in the spectrograms, and compared to the permutation testing on the uncorrected spectrograms, produces additional significant clusters and broadens the extent of the previous ones. Due to task design, it was not

possible to perform an associative memory contrast in this task. However, an analogous LCR contrast could be based on lure similarity, rather than the degree of memory strength, which would contrast memory interference, and likewise could be informative about theta's role in pattern separation. Nevertheless, such an approach was not feasible because it would further reduce the already small sample size of this study. A final consideration is that the majority of these studies reviewed investigated post-stimulus theta activity at retrieval. This study, in contrast, focused on encoding during both pre-stimulus and post-stimulus.

Prima facie, the pre-stimulus theta result also seems to be in disagreement with the existing literature assessing pre-stimulus theta activity, which has shown that pre-stimulus theta is associated with subsequent correct recognition. To make sense of this apparent discrepancy, it is important to first make note of the differences in task design. All studies showing this effect in humans have utilized variations of a word-recognition task. Two studies utilized variations on the incidental encoding task (for deep vs shallow processing) (Fellner et al., 2013; Guderian et al., 2009), and two others employed cue associations (Addante et al., 2011; Gruber et al., 2013), but each task essentially involved the initial encoding of a set of words followed by a test of word recognition. Critically, these word-recognition tasks did not vary the similarity of word stimuli, in contrast to the task in this study, which varies the similarity of images. This is an important difference because it introduces interference to the memory retrieval process: determining if you have seen a picture from a set of many images is much simpler if the images are easily distinguishable from one another, whereas, discriminating between two highly similar images can be difficult even if they are side by side – consider the common "spot the difference" children's

game. To address this, subsequent studies on the word-recognition task could increase memory interference by introducing similarities between some word pairs, e.g., using homophones or synonyms. Unfortunately, our data cannot be used to analyze the pre-stimulus theta effect in absence of interference from item similarity because false alarms are so rare on target stimuli.

This interference is the exact reason why such a paradigm was used to study pattern separation/completion in humans (Bakker et al., 2008; Lacy et al., 2011): the higher the similarity between paired stimuli, the greater the risk that the subsequent stimulus leads to a false alarm – possibly due to pattern completion in the hippocampus, while the lesser the similarity, the greater the likelihood that items are later discriminated – potentially facilitated by pattern separation in the hippocampus. So, considering this critical difference between the tasks, pre-stimulus theta may represent a preparatory brain state which biases the proximate encoding of a stimulus in such a way that it is prone to generalization. From the lens of theoretical neuroscience, perhaps the pre-stimulus theta brain state facilitates the encoding of a hippocampal index, but the index is not well orthogonalized, and so its later recall is biased toward pattern completion.

Notably, this effect is greatest for negative stimuli and highly obscured for the positive condition. This may be due to the emotional valence; however, recall that while many aspects of the stimuli were matched across emotion, the study could not control for arousal. Therefore, the stimulus categories might instead be considered as negative/high-arousal, neutral/low-arousal, and positive/mid-arousal. While negative/high arousal does show the greatest effect, neutral/low-arousal actually features a greater effect than positive/mid-arousal, so it seems the effect is not only driven by arousal, but possibly a

combination of both arousal and valence. While this is interesting to speculate about, it is not possible to make conclusions because the stimuli in this study were not accompanied by ratings for arousal, and even if they were stratifying the already small sample size of this dataset would severely impact statistical power as has been noted before. Likewise, to truly disentangle the effects of emotional valence and arousal, more data must be collected accompanied with the arousal level of each stimulus.

Another interesting matter for speculation is how this study might relate to clinical populations, especially with memory issues related to over-generalization. A prominent example are patients with post-traumatic stress disorder (PTSD), which is a mental illness driven by the over-generalization of a traumatic experience. PTSD has been shown to have an association with abnormalities in hippocampal structure and function (Akiki et al., 2017; Thomaes et al., 2013). Notably, a consistent finding among PTSD patients is an increase in theta relative to controls; remarkably, in mothers experiencing PTSD before delivery, their newborns also showed a similar relative increase in theta (Dunkley et al., 2015; Imperatori et al., 2014; Sanjuan et al., 2016; Veltmeyer et al., 2006). Historically, PTSD has been treated with anti-depressants and psychotherapy, but a promising new avenue for the treatment of PTSD involves the use of drugs that increase activation in the serotonergic systems of the brain more acutely than antidepressants, e.g., MDMA and psilocybin, in conjunction with intensive psychotherapy targeting the recontextualization of the trauma (Varker et al., 2020). Intriguingly, psilocybin and other psychedelics, MDMA, and endogenous serotonin activation, have all been linked to long-term potentiation mechanisms of neuroplasticity (Mlinar et al., n.d.; Morini et al., 2011; Raval et al., 2021); moreover, each of these have all been shown to decrease hippocampal theta rhythm in rats and rabbits (Frei et al., 2001;

Kudina et al., 2004; Lansbergen et al., 2010; Sörman et al., 2011). In addition, psilocybin has been shown to increase neurogenesis in the hippocampus and improve the rate of fear extinction in rats (Catlow et al., 2013); in contrast, MDMA may be neurotoxic and impair learning at recreational and therapeutic doses, but the findings are contentious (Gouzoulis-Mayfrank & Daumann, 2006). Taken together these studies suggest that PSTD may be a disease that biases the hippocampus toward pattern completion of stimuli vaguely resembling aspects of a subject's prior trauma, which may be mediated by increases in theta activity. Furthermore, the reconsolidation of this trauma in a safe context – perhaps aided by medication that enhances vividness of experience, increases neurogenesis & neuronal plasticity, and simultaneously reduces the theta rhythm – can restore the pattern-separation/completion balance in the hippocampus. Perhaps, the reduction in theta combined with the neurogenerative effects underlies the efficacy of these treatments in reconsolidating the trauma such that it can be properly discriminated from non-aversive stimuli, but many additional studies would be needed to test such speculation. With regard to this study, pre-stimulus theta may reflect to a baseline brain state which alters the processing of subsequent stimuli, so given that PTSD patients exhibit an elevated theta baseline and a propensity to overgeneralize, I would expect these subjects to demonstrate a greater incidence of LFA – especially to negative stimuli – accompanied by greater pre-stimulus theta power relative to healthy individuals. However, following treatment, I would anticipate that both performance and pre-stimulus theta activity approach those of healthy controls.

PTSD often presents comorbidly with depression and anxiety, which are also associated with over-generalization problems. The effect of depression was previously

examined using the same task in this study and it was shown that depressed individuals had impaired discrimination across emotional valence relative to controls, but notably, severity of depression was correlated with discrimination of negative stimuli and accompanied by increases in BOLD activity in the amygdala and decreases in activity of CA3/DG (Leal et al., 2017b). More generally, depression has been linked to reduced activity in the hippocampus of humans, and in addition has been correlated with the retraction of dendritic processes in CA3 and a reduction of neurogenesis in DG with rodent models (Sahay & Hen, 2007; Watanabe et al., 1992). However, the relationship between the theta rhythm and depression is unclear, with some studies showing increases and others decreases relative to controls (Fernández-Palleiro et al., 2019). Anxiety's effect on discrimination has been explored using other paradigms; for example, mice over-generalize freezing behavior from an aversive environment in which they receive foot shocks to safe environments that are similar (Kheirbek et al., 2012). In humans stress induced by random shocks during encoding improves subsequent discrimination ability if the retrieval occurs in a safe environment – presumably due to heightened arousal; however, the improvement is lost if retrieval is accompanied by the threat of shock, which may be indicative of anxiety causing overgeneralization by biasing pattern-completion over separation (Balderston et al., 2015). Interestingly, anxiety has been consistently shown to be accompanied with increased theta activity (Çalışkan & Stork, 2018; Cornwell et al., 2012; Jacinto et al., 2016). Additionally, antidepressants– some selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, in particular – which are used to treat depression and some manifestations of anxiety and PTSD, have been associated with an increase in neurogenesis (Planchez et al., 2020). As previously

mentioned, psychedelics also increase neurogenesis, and like PTSD, have been indicated as highly effective in the treatment of depression and anxiety (Muttoni et al., 2019). Unlike psychedelics, the effect of antidepressants on theta is not well-characterized. However, ketamine (esketamine), which was recently given an FDA Breakthrough Therapy Designation for treatment-resistant depression and suicidal behaviors, has been demonstrated to reduce theta power (Fitzgerald & Watson, 2019; Swainson et al., 2019). Considering these clinical and related pharmacological observations, further electrophysiological studies in these clinical populations could be informative towards the role of pre-stimulus theta in over-generalization. However, direct assessment of hippocampal theta in these subjects would depend on recruiting epilepsy patients with such comorbidities.

In summary, the hippocampus is critical for episodic memory and navigation – theoretically mediated by patten-separation/completion processes on hippocampal indices that link activations of neocortical network– and the theta rhythm plays an important role in this phenomenon. With this dissertation, I presented results from an image recognition task in humans with hippocampal recordings, and demonstrate that, during encoding, pre-stimulus theta is associated with over-generalization, while post-stimulus theta is related to proper discrimination; additionally, I found evidence that post-stimulus activity in higher frequencies is reduced coincident with the theta increase. Due to the small sample size, and some apparent disagreement with existing literature, these results await the support of additional studies. Nevertheless, these findings are an important supplement to a modest literature on pre-stimulus electrophysiological correlates of memory encoding and inform the ongoing debate on human hippocampal theta and memory.

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