

Saccadic Eye Movement Event-Related Potentials and the Effects of Subsequent Phase-Based Stimulation on Memory in Humans

by

Chaim N. Katz

A thesis submitted in conformity with the requirements
for the degree of Doctor of Philosophy

Institute of Biomedical Engineering
University of Toronto

© Copyright by Chaim N. Katz 2021

Saccadic Eye Movement Event-Related Potentials and the Effects of Subsequent Phase-Based Stimulation on Memory in Humans

Chaim N. Katz

Doctor of Philosophy

Institute of Biomedical Engineering
University of Toronto

2021

Abstract

With the ageing population comes an increase in dementia and memory-related disorders.

Investigations of memory formation can facilitate insights into more effective treatments for this growing problem. Deep brain stimulation (DBS), the delivery of electrical stimulation to modulate brain activity, presents an exciting opportunity to investigate mechanisms of memory formation and potentially alleviate memory loss. One critical question with regards to DBS is when and where to stimulate.

Treatment for individuals with epilepsy who require resection surgery usually involves the implantation of electrodes in mesial temporal lobe structures (MTL), locations known to be involved in memory formation. This provides a unique opportunity for researchers, in a controlled setting, to record and stimulate the brain to investigate memory formation. Episodic memory, our recollection of personal experiences, can be tested through visual cues (presenting a stimulus and saccadic eye movements (SEM) during memory task). We used a model of how the brain can separate encoding and retrieval states to inspire our approach to try and optimize DBS timing delivery. Our objectives were to 1. Determine which visual stimulus is most relevant for timing stimulation, and 2. Determine the effects of such stimulation.

In this thesis, we identified that eye movement in response to a visual stimulus is a more appropriate timing cue than image presentation. In fact, through work with single-unit activity, we found inhibition of activity during the SEM. Our results suggest the SEM in MTL results from an internally generated movement not previously probed in mnemonic structures. Finally, we were able to investigate the effects of contingent stimulation on the SEM. This stimulation resulted in memory impairment. By customizing stimulation delivery contingent on an individual's timing of the electrophysiological response post saccade, we saw no difference in memory performance between stimulation and no stimulation

We successfully established eye movements as an important timing mechanism in MTL structures. Furthermore, stimulation contingent on eye movements can modify memory. These contributions support the potential to look at eye movements as a window on stimulation for investigating, modifying, and hopefully improving memory formation.

Acknowledgments

The most important accomplishments in my life are much more representative of the people I have had the chance to work with and directly reflect the community in which I was raised. I want to acknowledge my friends, lab mates and family who have consistently supported me.

To my wife Lauren, when I started my graduate degrees 6 years ago, we hadn't even met, but now two degrees and a marriage later, you are still my constant, my everything and my whole world.

My parents have always been incredibly supportive of my pursuit of knowledge and constantly challenged me to ask questions. This encouragement has led to a simple phrase that many have heard me say, "You know what I don't understand." To them and my family, who continue to listen to my thoughts on the world, I am forever grateful.

To Cousins Kenny and Sheila and the whole Toronto family who provided me with a home away from home and ensured I had space and support to succeed.

To the Neuron To Brain Lab: Thank you for being a space to learn and grow with great people. Specifically, Homeira for being the lab mother, Victoria and her dedications to patients, Andrea for helping to ensure the work with single units went smoothly with constant re-edits, Marjan for always playing the music, Kramay for being an okay colleague, Gerard for sticking it through both Masters and Ph.D. and other lab mates from Neuron to Brain Lab with assistance on various aspects of the project.

Seriously though, Kramay, thank you for working with me on organizing multiple conferences, supporting multiple research works, S4C, and being there to bounce ideas off.

Without the clinical technicians, staff, and support team, I would not have completed this project.

Their patience and efforts are greatly appreciated.

The Ph.D. ends with a thesis, but I believe a genuinely successful Ph.D. has balance with meaningful events to each individual. Whether it be GECoS, S4C, Grad PACs, Purple Day and Epilepsy awareness, or any other extracurriculars I have been fortunate to participate in, I would like to acknowledge that I have worked with some fantastic people. Sumayya and Alex, thanks for your help and support with driving epilepsy awareness events. Esmeralda, thank you for being my constant support with GECoS. Thank you to all the volunteers who have dedicated their precious spare time to many of these endeavours.

To Dr. Hoffman, whose work provided a framework for this investigation and to Dr.

Talakoub who supported the work even after the move to a new institution.

To Dr. Duncan for support in the design of the task and constant meetings to discuss the psychological approach and appropriate stats. I hope to continue to improve my writing from our discussions.

To my committee, Dr. Katherine Duncan, Dr. José Zariffa, Dr. Paul Yoo, for their constant guidance throughout the project and considered me worthy of the degree.

To Dr. Suthana and Dr. Márquez Chin, thank you for serving as external examiners and providing me with your time and efforts to ensure the thesis and defence were a success.

To my co-supervisor, Dr. José Zariffa and Adaptive Neurorehabilitation Systems Lab, you have seen me go through undergraduate, Masters, Ph.D. and have been consistently available for questions on research and life. Thank you.

Finally, my supervisor Dr. Taufik A. Valiante has been consistent support over the last six years. As a clinician and a scientist, I have always been incredibly privileged to learn from you in various circumstances. Our lab has gone through tremendous growth, but you have always been very clear that the personnel are essential, and you make us a priority. I am thankful for the opportunity to pursue my Ph.D. and continue learning from you in the health care system. Thank you for being a mentor, a colleague, and a friend.

I am forever grateful to the epilepsy community and individuals with epilepsy with whom I was able to work. Although the research and learning are never complete, I am hopeful my project will take some steps towards making the world a better place and giving something back to that community.

Table of Contents

Contents

Acknowledgments.....	iv
Table of Contents.....	vii
List of Abbreviations	xii
List of Tables	xv
List of Figures.....	xvi
List of Appendices	xviii
Chapter 1.....	1
1 Introduction.....	1
1.1 Motivation.....	1
1.2 Approach.....	2
1.2.1 Determine which visual stimulus is most optimal for contingent stimulation.....	2
1.2.2 Effects of Stimulation	3
1.3 Organization of Thesis	3
Chapter 2.....	5
2 Literature Review.....	5
2.1 Ageing Population and Dementia Prevalence.....	5
2.1.1 Memory Disorders	7
2.2 Episodic Memory and MTL.....	9
2.3 Deep Brain Stimulation as a Treatment	13
2.3.1 DBS in Memory Related Disorders	14
2.3.2 Closing the Loop.....	26
2.4 Potential Natural Timing for Stimulation	27
2.4.1 Eye Movements and Memory.....	27

2.4.2	MTL and Oculomotor Connectivity	29
2.4.3	Phase Reset: Event-Related Potentials from Eye movements and Visual Presentation.....	30
2.4.4	SPEAR Model.....	32
2.5	Hypothesis and Objectives.....	35
Chapter 3	36
3	Visual Phase Reset for Optimal Stimulation Timing.....	36
3.1	Introduction.....	36
3.2	Methods.....	39
3.2.1	Method Details.....	39
3.2.2	Quantification and Statistical Analysis.....	50
3.3	Results.....	52
3.3.1	Visual Search Behaviour.....	52
3.3.2	Fixation vs Saccade Responses.....	52
3.3.3	Analysis and Removal of the Peri-Saccadic Transient.....	53
3.3.4	Event-Related Potentials (ERPs)	54
3.3.5	Phase Clustering.....	57
3.3.6	Power Changes.....	60
3.4	Discussion.....	62
3.4.1	Evoked Image-Onset Response	62
3.4.2	Phase-reset following Saccade Onset	63
3.4.3	Comparison of the two responses	66
3.4.4	Saccade related phase resetting is not an EOG artifact.....	68
3.5	Conclusion	68
3.6	Author Contributions	69
Chapter 4	70

4	Corollary Discharge: Eye Movement is an internally generated timing signal	70
4.1	Introduction.....	70
4.2	Methods.....	72
4.2.1	Participants.....	73
4.2.2	Experimental Design.....	73
4.2.3	Electrophysiology	75
4.2.4	Analysis of eye-tracking data.....	76
4.2.5	Analysis of electrophysiological data	77
4.3	Results.....	81
4.3.1	SUA within the MTL are modulated in the peri-saccadic interval.....	81
4.3.2	SEM related modulation is predominantly inhibitory	82
4.3.3	Saccadic modulation precedes SEM onset	83
4.3.4	The units and the response timing of the SEM-related SUA are distinct from those from image onset.....	84
4.3.5	Saccadic Modulation of the MTL varies with saccade direction.....	86
4.3.6	SEM related SU firing rate decreases correlate to post-saccade ERP amplitude ..	87
4.4	Discussion.....	89
4.4.1	Firing-rate decreases dominate the peri-saccade period.....	89
4.4.2	SU activity reflects the early arrival of spatial and temporal parameters of ensuing eye movement.....	91
4.4.3	SU modulated with saccades are distinct from units responsive to image onset...91	
4.4.4	Role of directional information in the MTL	92
4.4.5	Limitations of current work	93
4.5	Conclusion	94
5	Stimulation Effects on Memory	96
5.1	Introduction.....	96
5.2	Materials and Methods.....	99

5.2.1	Participants.....	99
5.2.2	Closed-Loop Deep Brain Stimulation System.....	103
5.2.3	Memory Task.....	106
5.2.4	Data Analysis.....	108
5.3	Results.....	110
5.3.1	Eye movements and stimulation.....	111
5.3.2	Effect of Stimulation Types on Recognition.....	112
5.3.3	Overall Memory Performance.....	112
5.3.4	Effect of stimulation types on memory across the group.....	113
5.3.5	Effect of timing customization on memory.....	114
5.4	Discussion.....	115
5.5	Conclusion.....	119
Chapter 6	120
6	Discussion.....	120
6.1	Saccadic Modulation as Timing in The Hippocampus.....	120
6.1.1	Phase Reset through Local Field Potential (LFP).....	121
6.1.2	Corollary Discharge through Single Unit Activity.....	122
6.2	Stimulation Contingent on Eye Movements and Theta Phase Reset.....	125
6.2.1	Saccadic ERP Based stimulation.....	125
6.3	Findings Fit Within Literature on Theta.....	126
6.3.1	Theta and Memory.....	126
6.3.2	Brain States.....	127
6.4	Primary Limitations.....	128
6.4.1	Stimulation Parameters.....	128
6.4.2	Data Variability.....	129
6.5	Future Directions.....	129

Chapter 7.....	134
7 Conclusion.....	134
References.....	136
8 Appendices.....	180
8.1 Appendix A- Supplementary Items Chapter 3.....	180
8.1.1 Figure S1.....	180
8.1.2 Figure S2.....	181
8.1.3 Figure S3.....	182
8.1.4 Figure S4.....	183
8.1.5 Figure S5.....	184
8.1.6 Figure S6.....	186
8.1.7 Figure S7.....	188
8.2 Appendix B- Supplementary Items Chapter 4.....	189
8.2.1 Figure S1.....	189
8.2.2 Figure S2.....	191
8.2.3 Figure S3.....	192
8.2.4 Figure S4.....	193

List of Abbreviations

ADAS-Cog	Alzheimer's Disease Assessment Scale, Cognitive Subscale
BS	Broad Spiking
CA	Cornu Ammonis
CCEP	Cortico-Cortical Evoked Potentials
CD	Corollary Discharge
CDR-SB	Clinical Dementia Rating Sum Of Boxes
CSRT	Coetsier Story Recall Test
CVLT	California Verbal Learning Test
DG	Dentate Gyrus
DBS	Deep Brain Stimulation
DL-PFC	Dorsolateral Prefrontal Cortex
EC	Entorhinal Cortex
EEG	Electroencephalography
EOG	Electrooculography
EMU	Epilepsy Monitoring Unit
ERP	Event Related Potential
FDR	False Discovery Rate
FEF	Frontal Eye Fields
FF	Future Field
GPI	Globus Pallidus Internal
HC	Hippocampus
HF	High-Frequency Stimulation
HS	Hippocampal Sclerosis
ICA	Independent Component Analysis
IDT	Identification by Dispersion-Threshold
iEEG	Intracranial Electroencephalography
ITI	Inter Trial Interval
ITPC	Inter Trial Phase Coherence
IVT	Identification by Velocity-Threshold

LF	Low-Frequency Stimulation
LFP	Local Field Potential
LTD	Long Term Depression
LTP	Long Term Potentiation
MIMO	Multi-Input-Multi-Output
MMSE	Mini-Mental State Examination
MTL	Mesial Temporal Lobe
MUA	Multi-Unit Activity
NS	Narrow Spiking
NBM	Nucleus Basalis of Meynert
NHP	Non-Human Primates
NMDA	N-Methyl-D-Aspartate
NPI	Neuropsychiatric Inventory
PCC	Posterior Cingulate Cortex
PD	Parkinson's Disease
PHG	Parahippocampal Gyrus
RAVLT	Rey Auditory-Verbal Learning Task
RF	Receptive Field
RMS	Root Mean Squared
RVDT	Rey Visual Design Test
SEM	Saccadic Eye Movement
SD	Saccade Direction
SFG	Superior Frontal Gyrus
SME	Subsequent Memory Effect
SPEAR-	Separate Phases Of Encoding And Retrieval
stFFT	Short-Time Fast-Fourier Transform
SUA	Single Unit Activity
STN	Subthalamic Nucleus
TBS	Theta Burst Stimulation
TC	Temporal Cortex
TLE	Temporal Lobe Epilepsy
TSP	Trisynaptic Pathway

(VAF)	Variance-Accounted-For
WCST	Wisconsin Card Sorting Test
WHO	World Health Organization

List of Tables

Table 2.1 Four reports detailing the increasing prevalence of Dementia in Canada.	6
Table 2.2 Continuous Open Loop Stimulation Studies.....	18
Table 2.3 Conditional Open Loop Studies.....	22
Table 3.1 Patient Summary Table.....	39
Table 3.2 Time-frequency window definitions.....	49
Table 4.1 Participant summary table.....	73
Table 5.1 Participant Summary table.	100

List of Figures

Figure 2.1 Age pyramid.	6
Figure 2.2 Example taxonomy of brain systems underlying memory.	10
Figure 2.3 Hippocampal circuitry	13
Figure 2.4 Anatomical targets for DBS for memory.....	14
Figure 2.5 Schematics showing different types of DBS	16
Figure 2.6 Oscillations and proposed functionality	31
Figure 3.1 Behavioural task and fixation detection	42
Figure 3.2 Saccade vs. fixation alignment of hippocampal response to eye movements	45
Figure 3.3 Event-related potentials (ERPs) following saccade and image onset.....	56
Figure 3.4 Theta phase reset simulation.....	57
Figure 3.5 Intertrial phase clustering (ITPC) for hippocampal electrodes.....	59
Figure 3.6 Spectral power for saccade-onset and image-onset epochs for hippocampal electrodes	61
Figure 4.1 Behavioral task and recording locations.....	75
Figure 4.2 Categories and distribution of modulated units	80
Figure 4.3 Broad spiking units largely demonstrate decreases in firing rate	83
Figure 4.4 MTL units modulated following image onset are distinct from those modulated during SEMs	85
Figure 4.5 SEM-related SUA and ERPS are directionally modulated and correlated to one another.....	88
Figure 5.1 Example of theta-burst stimulation protocol	105

Figure 5.2 Behavioural task	108
Figure 5.3 Extracting timing of stimulation.....	111
Figure 5.4 Stimulation and Saccade Event Distributions Based on Stimulation Type	112
Figure 5.5 Group memory performance.....	113
Figure 5.6 Customization effects on behavioural performance	115
Figure 6.1 Closed Loop Stimulation Considerations	131
Figure S8.1 Representative distribution of peri-saccadic artifact magnitude	180
Figure S8.2 Spatial distribution of peri-saccadic artifact and saccade-onset response magnitude	181
Figure S8.3 Event-related potentials (ERPs) for blinks	182
Figure S8.4 Event-related potentials (ERPs) for parahippocampal electrodes	183
Figure S8.5 Intertrial phase clustering (ITPC) for saccade onset and image onset for parahippocampal electrodes.....	184
Figure S8.6 Spectral power for saccade-onset and image-onset epochs for parahippocampal electrodes	186
Figure S8.7 Consistency of ERP for saccade onset and image onset across different trials.....	188
Figure S8.8 Modulatory effects in Occipital areas.....	189
Figure S8.9 Modulatory effects are similar within different areas of the MTL.....	191
Figure S8.10 Multiple Unit Activity (MUA) of units modulated by image onset.....	192
Figure S8.11 Characteristics of directional modulation in the MTL	193

List of Appendices

Appendix A- Supplementary Items Chapter 4

Appendix B- Supplementary Items Chapter 5

1 Introduction

1.1 Motivation

Memory impairment represents a major healthcare issue. Dementia, specifically, is characterized by a decline or difficulties in memory, language, problem-solving and other cognitive skills that can affect an individual's ability to perform routine activities[1]. The *Diagnostic and Statistical Manual of Mental Disorders* classifies it as a major neurocognitive disorder because it interferes with both cognitive function and performing everyday activities[2]. In the United States, one in ten people 65 and older have Alzheimer's Dementia[3]. The Alzheimer's Society predicts that in Canada, 912,000 people will have dementia by 2031, and at least 1.1 million people are currently impacted[4]. One of the most comprehensive worldwide reports, still used by the World Health Organization(WHO) today, suggests that in 2015, the total global societal cost of dementia was \$818 billion, which is the equivalent of 1.1% of the gross domestic product at that time[5]. Thus, the societal and economic burden of dementia is immense. Such a situation drives demand for new drugs and interventional therapies to manage the symptoms and slow, if not entirely halt, the disease's progression[6].

One innovative treatment option for dementia is deep brain stimulation (DBS)[7]. DBS is a clinically validated approach that uses electrical stimulation to modify cell and circuit activity[8]. In the context of dementia, DBS represents a potentially promising clinical treatment given its history in treating other neurological diseases[9]–[11] and early work in humans[12]–[15] and animals[16]–[21]. Given the ease of access to the rodent and nonhuman primate (NHP) brain for invasive investigations, much of what we understand electrophysiologically about the memory process processes are derived from such studies. However, declarative memory, or consciously recalled memory, is of particular translational relevance and is most easily tested in humans.

Given the critical role of the mesial temporal lobe (MTL) and specifically the hippocampus in declarative memory[22], it has been a natural target for electrical stimulation to augment human memory[23]–[25]. Some studies have shown improvement[12], [26], although the vast majority of direct electrical stimulation of the hippocampus in humans degrades memory[24], [25], [27]–[30]. Much of the literature consists of open-loop stimulation, including a current major clinical trial[31]. Open-loop stimulation means that stimulation is delivered without taking into account the underlying neural activity. Hence, a major challenge in the literature is identifying the appropriate stimulation timing to maximize its effectiveness. In this way, stimulation parameters can be adapted effectively during natural memory formation.

1.2 Approach

Our approach to addressing stimulation timing consists of two major components:

1. Determine which visual stimulus is most relevant for timing stimulation
2. Determine the effects of such stimulation

1.2.1 Determine which visual stimulus is most optimal for contingent stimulation

It is possible to record neurological activity while participants perform a visual memory task. Visual memory tasks involve presenting a stimulus (e.g. scene, face, drawing) and the subsequent assessment of previously presented stimuli with new ones. Both eye movements and initial presentation of the stimulus elicit a neurological response in MTL structures. Therefore, the timing of electrical stimulation of the MTL could be based on the initial presentation of a stimulus or on the ongoing eye movements during the processing of the stimulus. Electrical stimulation has only been timed to image presentation with mixed results.

Recording from MTL structures during a memory task that results in both eye movements and image presentation will support which stimulus is optimal for timing electrical stimulation. Both the large-scale brain activity and single-unit activity can inform on the mechanism that generates a specific neurological response. In particular, a neurological response called a phase reset is

considered a vital timing mechanism in the brain. Therefore, we determine which neurological response should be explored to effectively time electrical stimulation.

1.2.2 Effects of Stimulation

Once the timing strategy has been determined, the impact of this closed-loop stimulation on memory performance is investigated.

1.3 Organization of Thesis

The thesis is divided into three separate paper submissions, which can be read independently. However, the document is organized to ensure logical flow as follows.

Chapter 2 provides an overview of the literature and relevant work. Specifically, it establishes memory impairment as a critical issue where DBS might be a possible treatment. The current inconsistent results are discussed in the context of what is known about memory formation. In particular, the eye movements and memory systems seem to be interconnected structurally and functionally. One mechanism involved in memory formation, synaptic plasticity, has been explored using contingent stimulation based on the peak or trough of an event-related potential (ERP) in the MTL in response to a stimulus. Visual responses and eye movements can both elicit an ERP in MTL structures. The literature suggests that further work is needed to establish which ERP in the human MTL can be used for closed-loop stimulation. Subsequently, our hypothesis and objectives are presented.

Chapter 3 describes an investigation into whether an eye movement-related response or image presentation results in a phase reset in the human MTL.

Chapter 4 describes a further investigation of the single-unit activity and what this means for the mechanism underlying the response to eye movement in the MTL.

Chapter 5 describes a study assessing the effects on memory of stimulating based on a naturally occurring ERP.

Chapter 6 provides an overall discussion of the results, their implications for the future, and the limitations of the work.

Chapter 7 provides summarized main conclusions and a few future studies to consider.

2 Literature Review

2.1 Ageing Population and Dementia Prevalence

The United Nations indicated that in 2020, there were over 727 million people worldwide over the age of 65[32]. Current estimates suggest that this number will double by 2050, and the proportional population will increase from 9.3% to 16% in 2050[32]. Such trends are also evident in Canada. For example, in 1971, only 8% of Canada's population was over 65, and as of 2020, that number is 18%[33]. This ageing problem is commonly referred to as the inversion of the age pyramid. (Figure 2.1) People live longer and comprise a larger share of the overall world population. With the reality of an ageing population come many healthcare issues. One primary concern is dementia. According to the World Health Organization, 5-8% of people over 60 can have dementia[34], leading to a prevalence of around 50 million people, with nearly 10 million new cases every year worldwide[1].

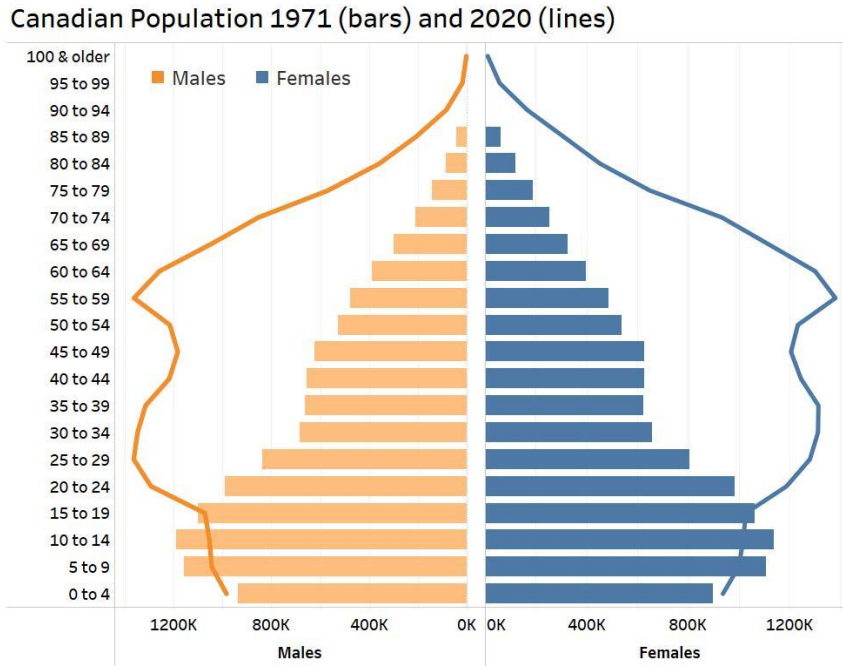


Figure 2.1| Age pyramid: From 1971 and 2020 detailing the Canadian population's shifting age demographics. Data retrieved from [33].

In 2016 the Alzheimer Society of Canada (www.alzheimer.ca) compared four reports that provided estimates of present and future prevalence of dementia in Canada[4] (Table 2.1). While the estimates vary based on data sources and inclusion criteria, consistent across all these reports is that prevalence of dementia will approximately double over two decades, and this trend will continue in years to come. Such an increase is a healthcare issue and a societal issue in ensuring that people retain their independence as they age and have proper support. These numbers are also an extreme economic concern. Treating dementia involves direct healthcare costs and indirect costs like informal caregiving and research into potential treatments. One of the most recent comprehensive analyses suggests that the total global societal cost of dementia was \$818 billion, which is the equivalent of 1.1% of the gross domestic product at that time[5].

Table 2.1| Four reports detailing the increasing prevalence of Dementia in Canada. The report projections include their group, age and projected population in Canada with dementia. The Mental Health Commission

of Canada, 2011 (MHCC). The Alzheimer Society of Canada, 2010 (Rising Tide); The National Population Health Study of Neurological Conditions, 2014 (NPHSNC); the CSHA, 1994; Adapted from [4].

Report	Ages	2011	2021	2031
MHCC[35]	>=55	747,129	1,024,465	1,435,923
Rising Tide[36]	All ages	521,280	687,552	923,763
CSHA[37]	>=65	480,000	600,000	780,000
NPHSNC[38]	>=40	340,170	461,651	673,991

2.1.1 Memory Disorders

Alzheimer's disease, the most prevalent form of dementia, may contribute to 60–70% of total dementia cases. One of the most problematic and common symptoms of Alzheimer's is amnesia, which typically includes impairment of learning or recall of recently learned information. Other common forms of Alzheimer's, which may not involve amnesiac presentation, include posterior cortical atrophy[39], logopenic-primary progressive aphasia[40], and executive dysfunction-frontal variant[41]. The primary symptoms involve language issues, visual issues, or executive dysfunction, respectively. In addition to such symptoms, those who suffer from dementia can also have other co-morbidities, including depression[42] and anxiety[43].

Dementia has specific clinical criteria used for indicating it as a symptom. A working group of the United States National Institute of Aging/Alzheimer's Association[44] refined these criteria for clinical use. The criteria include cognitive and behavioural symptoms that interfere with work or usual social activities, represent a decline from prior levels of functioning, and cannot be explained by delirium or another major psychiatric disorder. Detecting dementia requires rigorous history taking and objective cognitive assessment. Finally, the cognitive and behaviour impairment must include at least two of the following:

- Impaired ability to acquire and remember new information
- Impaired reasoning and handling of complex tasks

- Impaired visual-spatial abilities
- Impaired language functions
- Changes in personality/usual character, impaired motivation initiative

Even though Alzheimer's disease is the most prevalent subtype of dementia, other dementias and memory-related conditions are debilitating to an individual. Some examples include Lewy Body disease[45], frontotemporal dementia variants[46]–[48], and even chronic traumatic encephalopathy[49]. Different pathologies exist for different dementias and require various treatments and considerations. Other neurological conditions can even present with dementia-related symptoms. Unfortunately, there is no cure for these diseases, and most treatments address some of the underlying symptoms[50].

For example, one pharmacological approach in Alzheimer's disease involves cholinesterase inhibitors. Their use is designed to increase acetylcholine in brain structures, with the intent to improve cognition, with minimal success[51]. Other drugs or even non-pharmacological therapies assist with mood and other neuropsychiatric symptoms[52]. Therefore, it is imperative to find a treatment that can work in the long term for memory-related symptoms. Any further insights into mechanisms of memory formation and possible remedies have the potential to help affected individuals and alleviate the economic burden.

Interestingly, Parkinson's disease (PD) and epilepsy are two neurological conditions that can provide critical insight into memory research.

PD is typically associated with uncontrollable tremors. However, PD also presents with memory effects[53]. Dementia-related symptoms exist in 75% of PD patients at ten years and 87% at 20 years[54]. Such estimates are concerning since PD prevalence itself is also expected to double by 2040[55]. One possible cause involves the brain structures affected by PD. For example, Braak staging consists of disease spread to the mesial temporal lobe (MTL) for both PD[56] and Alzheimer's[57], an area thought to be involved with memory.

Individuals with epilepsy can have their seizures originate from these MTL structures. Epilepsy is a neurological condition associated with seizures, occurring in approximately 0.6% of

Canadians and about 1% of the population worldwide[58],[59]. Approximately one-third of individuals with epilepsy become drug-resistant and require alternative treatments for alleviating seizures[58]. In addition to seizures, individuals with epilepsy exhibit degraded executive function and performance on intelligence measures[60]. Specifically, with temporal lobe epilepsy (TLE), where seizures originate from temporal lobe structures, patients can present remarkable memory deficits[61].

Individuals with medically intractable epilepsy are candidates for diagnostic and subsequent therapeutic (resective) surgery to eliminate seizures or reduce seizure frequency. One diagnostic procedure to determine resective surgical candidacy is intracranial electroencephalography (iEEG). This technique allows for the placement of electrodes that can both record and stimulate deep brain structures. The use of iEEG in individuals with epilepsy thus provides a unique opportunity for research into memory-related brain structures and mechanisms of memory formation.

2.2 Episodic Memory and MTL

A foundational finding in cognition and memory research involved an individual with epilepsy, known as H.M. As part of H.M.'s treatment for seizures, he had both hippocampi structures in the MTL removed. Removing these structures resulted in the loss of much of H.M.'s explicit memory post-surgery; specifically, he could not encode specific types of new memories[22]. Such studies inspired further research and experimental work into how these structures establish the hippocampus's role in memory[62]. From these studies, various memory frameworks were identified (See Figure 2.2 for an example of one taxonomy)

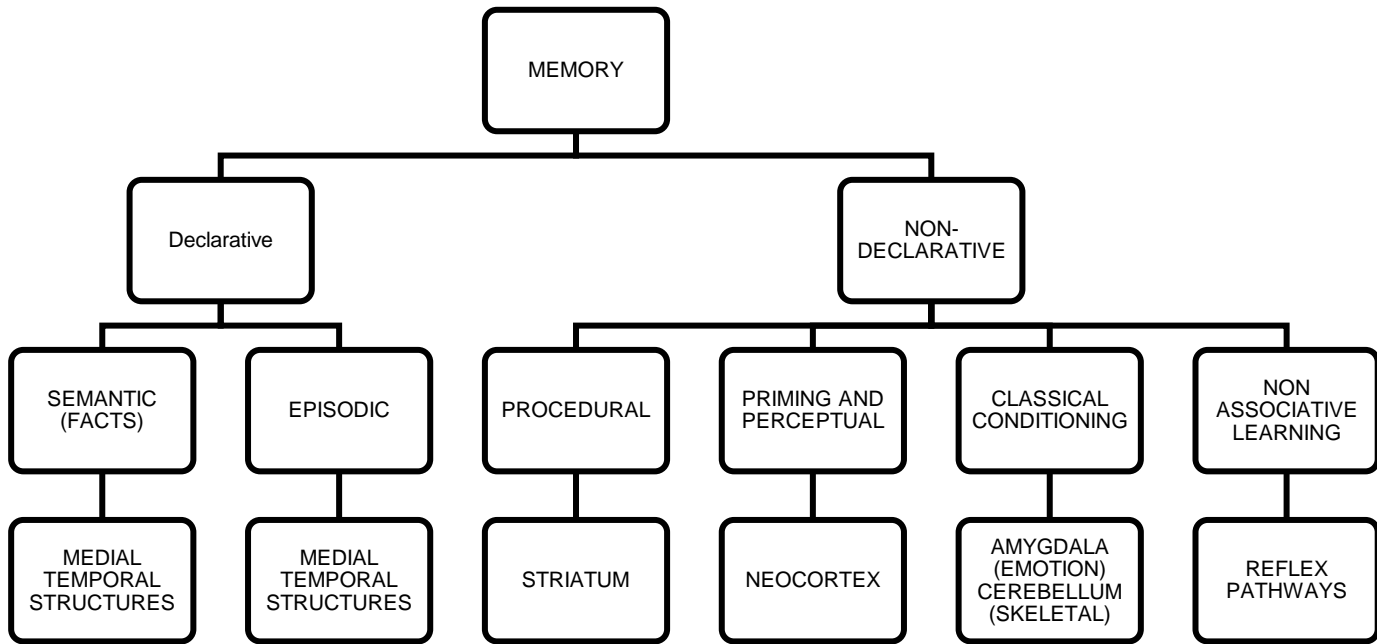


Figure 2.2 | Example taxonomy of brain systems underlying memory: Demonstrates division of memory into declarative and non-declarative forms and the respective anatomical locations believed to be primarily associated with each type of memory. Specifically, medial temporal structures are under the declarative memory category. Adapted with permission from Squire[63] and used in [64].

Under the taxonomy in Figure 2.2, MTL is considered part of consciously aware, declarative memory. Specifically, one of the most relevant types of human memory is our personal experiences. Tulving first proposed a categorization of episodic memory in 1972, which has been further refined over the years to include self-experiences and subjective time[65][66]. Episodic memory allows us to rapidly store personal events in such detail that they can be reexperienced[67]. To successfully orchestrate such an impressive feat, the brain must disentangle the relived past with the ever-evolving present. Indeed, failing to separate internally reactivated content from information arriving from the external world is thought to drive interference between old memories and new learning. The MTL and specifically the hippocampus are believed to be involved in such pattern separation of details to discriminate similar experiences[68].

The hippocampus's anatomical structure has been extensively researched to understand how it might be involved in memory processes. The hippocampus has various anatomical divisions, including the Cornu Ammonis (CA) fields (CA1 and CA3), the dentate gyrus (DG), and the subiculum that play different memory processing roles. Information about the external environment arises from the entorhinal cortex (EC), the primary cortical input to the hippocampus. This input arrives into the hippocampus through the EC in what is known as the perforant pathway. There are two primary pathways, the monosynaptic path, directly from EC to CA1 and the trisynaptic pathway (TSP), which connects to the dentate gyrus, subsequently projects to the CA3, which then projects to the CA1 and outputs to EC through the subiculum[69] (Figure 2.3).

These two pathways allow for stimuli that co-occur in time and space to be stored together while maintaining separate, distinct representations for similar stimuli[70]. Stimuli along the TSP are assigned distinct sparse cell assemblies. Simultaneously, the monosynaptic path allows for greater overlap of neuronal activation for encoding a stimulus to be learned over a longer time[71]. The principal neurons within the CA3 have broad recurrent connections involving excitatory glutamatergic synapses. These auto-associative connections can spread out an input across all elements of a previously activated network, enabling the putatively ascribed function of “pattern completion”[68], [72]. Therefore, when cued by a part of a memory, these connections allow for reactivation and reinstatement of previously activated representations. Subsequently, these recalled assemblies can be compared with the encoded input where CA1 can act as a comparator[73]–[76].

Critically, as described through the monosynaptic path and TSP, both regions synapse on neurons in the hippocampal CA1 subfield, which provide the hippocampus's primary output. Furthermore, the hippocampus receives convergent fibres from virtually all cortical association areas (and numerous subcortical structures)[69]. These connections within the structure and projecting to the cortex enable the processing of high-level perceptual information from diverse cortical regions.

Output from the hippocampus is believed to store declarative memory and bind it to neocortical networks in what is now known as standard consolidation theory[70], [77], [78]. Originally

thought to be only involved in consolidating memory for permanent storage, multiple trace theories suggest that the hippocampus acts as a pointer to encode and retrieve memories each time they are activated[79]. These frameworks lead to a concept of activation of specific cells during encoding of a stimulus and subsequent reactivation of cells during recollection in what is called a memory engram[80].

Semon originally defined an engram as “the enduring though primarily latent modification in the irritable substance produced by a stimulus” (For a review of the history of the engram, see[81]). Neurons that fire together can continue to strengthen their connections and represent a stimulus. This mechanism is summarized by the most basic form of memory, Hebbian learning, with the quote: “Neurons that fire together wire together”[82]. The hippocampus cellular structure even helps to facilitate such connections through N-Methyl-D-Aspartate (NMDA) mediated synaptic plasticity. NMDA is involved in weakening or strengthening the neuronal response depending on the respective input and is linked to memory[83]. Such synaptic plasticity is predicated on the necessity of both pre-and postsynaptic activity occurring and precise relative timing, resulting in strengthening the cells' synaptic connection. This timing allows for modifications to neuronal firing patterns when achieved across distributed brain networks that can support memory engram formation.

Not only does it seem that the hippocampus is involved with explicit memory testing[68], [84], [85], but it is also involved in association with spatial location[86]–[88]. Recently, it has been proposed that the hippocampus is involved in connecting items in space and time[89], [90]. Such an idea is further supported by specific neurons firing preferentially to time[91] and space[92], [93] in the hippocampus.

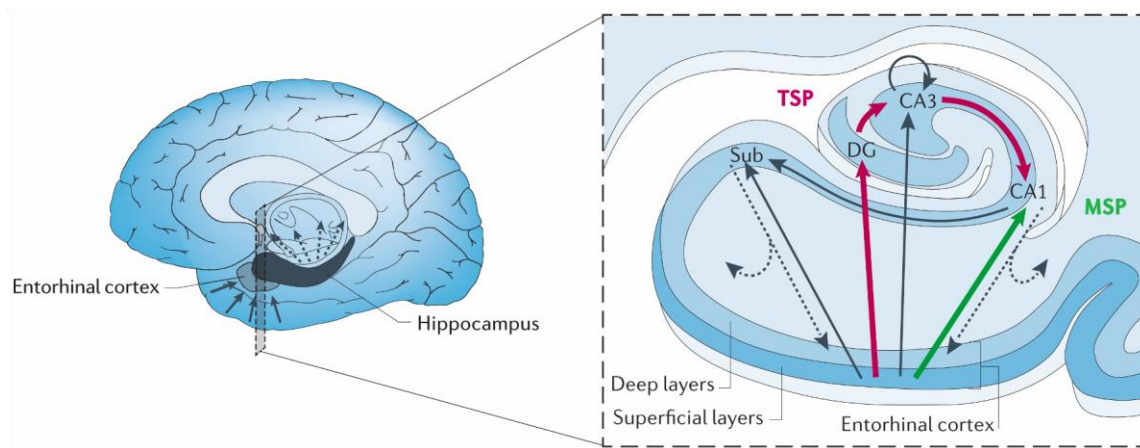


Figure 2.3 | Hippocampal circuitry: The hippocampus is depicted in a coronal slice. Inputs are in solid arrows, while outputs are dashed. The inputs are subdivided into TSP (pink) and monosynaptic pathways (green). The TSP operates dentate gyrus (DG) and CA3 to CA1, and the monosynaptic pathway directly to CA1. Obtained with permission from [89], [94]

2.3 Deep Brain Stimulation as a Treatment

The electrodes placed for monitoring brain activity can also be used for stimulation. Deep brain stimulation (DBS) has been used in various neurological conditions[95]–[97]. External electrical input modulates neural activity to interact with the brain in a controllable dynamic manner. Such stimulation allows for the investigation of the brain causally and can modulate pathological activity.

These types of stimulation were used for mapping but have also been previously used in treating neurological diseases. One of the first instances of this approach treating neurological conditions involved work by Dr. Robert Heath in the 1950s[11]. A book further describing this largely forgotten research has recently been written[98].

In PD, one of the largest clinical success stories employed DBS to specifically deliver high-frequency electrical stimulation to the subthalamic nucleus (STN) or the globus pallidus internal (GPi)[99]. The mechanism is not fully understood, but stimulation targeting PD's pathological structures, the cortico-basal ganglia network, is critical. Therefore, perhaps one of the most important elements for success is targeting the appropriate location.

2.3.1 DBS in Memory Related Disorders

Given the use of DBS for various neurological conditions, it was even proposed that it be used to help regulate overeating in a morbidly obese individual[100]. Placing the electrodes in the hypothalamus, a structure known for its role in regulation, the intent was to regulate eating. Serendipitously, stimulation helped improve the individual's memory. Upon further review, the stimulation was impacting the fornix rather than the initially intended hypothalamus.

The fornix, in fact, provides significant input to the hippocampus, which connects the hippocampus to an extensive array of cortical and subcortical structures[101]. It is part of a larger Papez circuit (a neural circuit proposed by James Papez in 1937), which is thought to be also responsible for declarative memory function (Figure 4). The Papez circuit includes the fornix, hypothalamus, hippocampus, and anterior thalamic nuclei, which are key elements[102] believed to be targeted during such fornix/hypothalamus stimulation[15]. It is not surprising then that these structures are primary anatomical targets for stimulation to modulate memory.

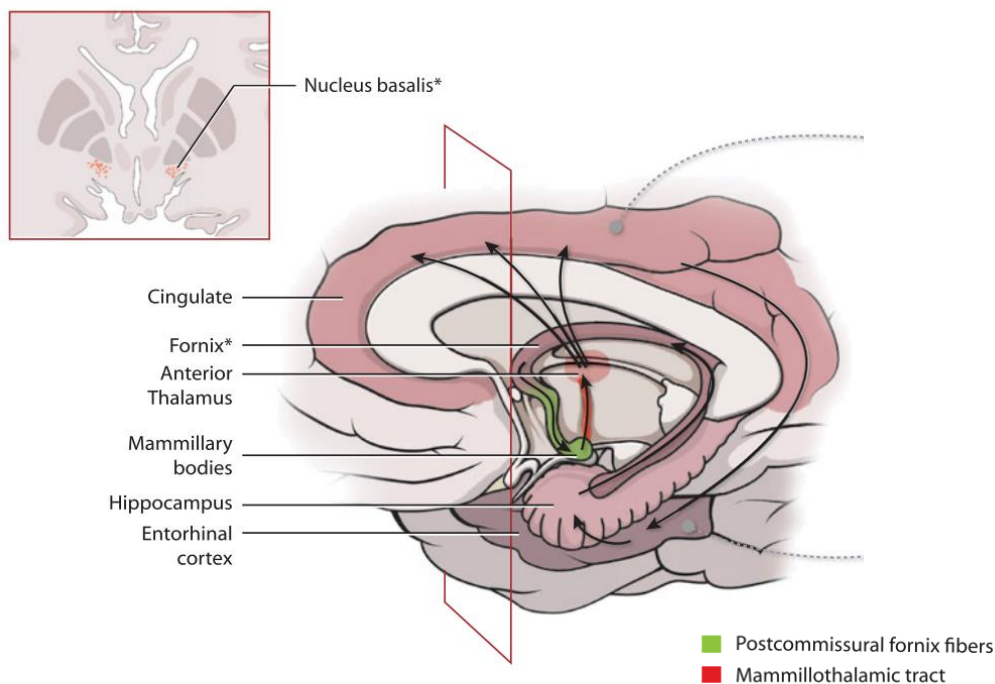


Figure 2.4 | Anatomical targets for DBS for memory: As part of the Papez circuit, many of these anatomical locations are considered promising targets for deep brain stimulation for memory. The fornix is a major pathway to the hippocampus governing memory and cognition. Neocortical projections from cingulate to the

default mode network (parietal, temporal, and frontal) provide feedback to the hippocampal formation. The portion of the fornix beyond the anterior commissure is known as the postcommissural fornix and is shown in green. Just inferior to the anterior commissure is the acetylcholine-rich nucleus basalis, which can cholinergically innervate the hippocampal formation. The mammillothalamic tract shown in red identifies connections from mammillary bodies to the anterior thalamic nucleus. These target locations are discussed in detail in [64], but here we focus on the MTL. (Obtained with permission from[8] and also used in [64].

In describing the approaches to deep brain stimulation for memory, we recently proposed that it is important to separate these approaches into three classes based on stimulation timing[64]. Continuous open-loop stimulation (Figure 2.5A) is typically used experimentally and clinically, where stimulation is delivered agnostic to the underlying neural activity or ongoing task. Conditional open-loop stimulation (Figure 2.5B) is delivered based on the timing of a stimulus presentation but agnostic to the underlying neural activity. Finally, and more recently, closed-loop stimulation considers both the ongoing task and the underlying neural activity (Figure 2.5C). These activities will be described briefly in relation to their impact on memory formation. (For a deeper review, see [64]).

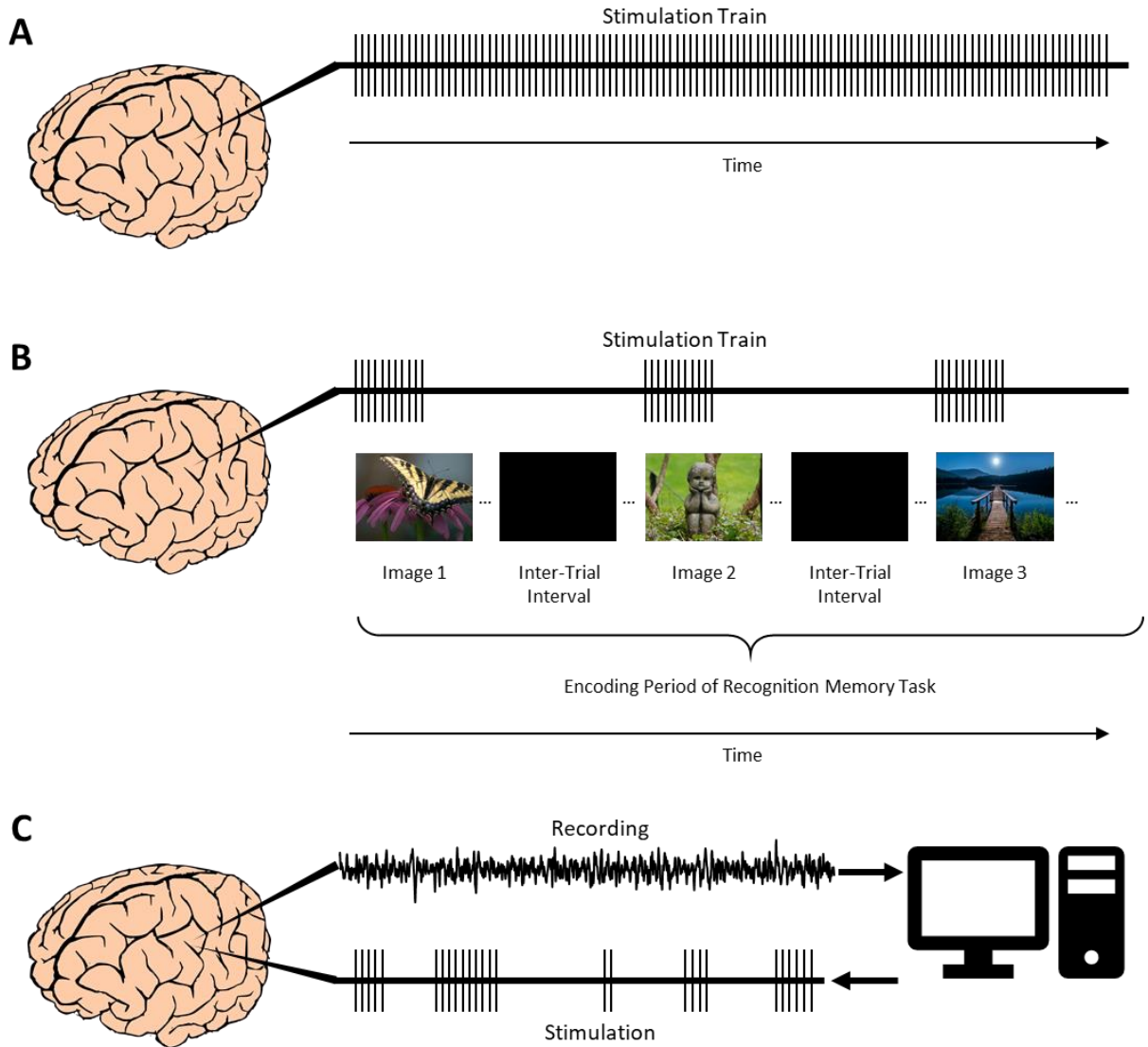


Figure 2.5 | Schematics showing different types of DBS: A) A Continuous Open Loop approach in which stimulation is delivered continuously. B) A Conditional Open Loop approach in which the stimulation is delivered in an open-loop manner but contingent on the ongoing memory task. C) A Closed-loop approach in which the stimulation is delivered contingent on underlying brain activity. Figure also used in [64] created by Kramay Patel.

Open Loop Stimulation

Controllers that do not receive any feedback from the system are known as open loop.

Functionally, an open-loop system will deliver electrical stimulus that can affect the brain state,

but the control system will not respond to these changes. These systems are primarily used in clinical trials as they are easiest to implement and test in natural settings. This stimulation type's primary features are the location and the stimulation waveform characteristics because of the lack of feedback.

The primary targets for open-loop stimulation have been the Papez circuit, including the fornix[15], [103], Nucleus Basalis of Meynert[104]–[106], the anterior thalamic nucleus[107], and MTL structures[23], [108]–[111]. (For a complete review, see chapter [64]and Table 2.2)

Since MTL structures are considered critical to declarative memory, it is not surprising that they are the primary targets of such research. Typically, participants in these studies are individuals with medically refractory epilepsy since such systems can stimulate to control seizures. One such study showed a reduction in seizures and a slight trend towards memory improvement[108]. Following chronic open-loop stimulation of the amygdalohippocampal formation, there was no improvement[111]. Such stimulation at an amplitude sufficient to trigger after-discharges has been shown to significantly impair late-recall performance in a verbal memory task[28]. High amplitude stimulation of the hippocampus can lead to impairment of visual and verbal memory, which can be rescued simply by reducing stimulation amplitude[110]. Therefore, based on current research into open-loop stimulation of MTL structures, memory can be affected but not typically improved.

Table 2.2| Continuous Open Loop Stimulation Studies- This table provides a summary of all the continuous open-loop stimulation studies discussed in this chapter, including an overview of the methods implemented in each study along with the relevant behavioural outcomes. California Verbal Learning Test (CVLT), Rey Auditory-Verbal Learning Task (RAVLT), the Rey Visual Design Test (RVDT), and the Verbal and Visuospatial Supraspan, Alzheimer’s Disease Assessment Scale, Cognitive Subscale (ADAS-Cog), Mini-Mental State Examination (MMSE), Coetsier Story Recall Test (CSRT), Clinical Dementia Rating Sum of Boxes(CDR-SB), Neuropsychiatric Inventory(NPI), Nucleus Basalis of Meynert (NBM), Wisconsin Card Sorting Test (WCST), Subthalamic nucleus (STN). (Also used in [64])

Year	n	Memory-related Outcome	Memory Task/Memory Type	Stimulation Location	Stimulation Parameters	Additional Notes/Details	Ref
1996	9	Impairment	Recognition task (Words and Block designs)	MTL Structures	3 V, 2.5ms Pulse width at 2 Hz	Stimulation applied starting 3 hours prior and during the task	[23]
2007	9	Improvement	Rey verbal learning; digit counting; logic memory, and Wind Mill visual-spatial Bezarez test	HC	0.3mA, 0.45ms pulse width at 130Hz	Stimulation was delivered for one minute every five minutes. In half of the subjects, stimulation started immediately after implant, and others one month later. Testing was done every three months for 18 months	[108]
2008	1	Improvement	CVLT, Spatial Associative Learning Task, Wechsler memory Behavioral Evaluation	Hypothalamus	2.8V, 0.06ms pulse width at 130 Hz	Performance on CVLT improved significantly after three weeks of continuous stimulation. The effect of stimulation was further characterized using tasks with high sensitivity and specificity for hippocampal function. These tasks were completed in a double-blind manner, with on-stimulation and off-stimulation periods separated by one week or 1 hour. In both these tests, the recollection index was significantly higher in the on vs. off stimulation period.	[100]
2009	1	Improvement in AVL T	Letter-Number-Span test, Digit Symbol Test, Trail Making Test Part B, Rey Auditory Verbal Learning Test (AVLT)	STN and NBM	4.2V at 0.06ms pulse width at 130Hz (STN) 1V at 0.12ms pulse width at 20Hz (NBM)	Testing one week before implanting the electrodes, after DBS in 4 double-blind phases: STN stimulation, combined STN and NBM stimulation, STN stimulation, and combined STN and NBM. Taking away the NBM stimulation in phase 3 resulted in a significant decline in cognitive and memory performance, which was rescued by resuming NBM stimulation in phase 4.	[104]
2010	6	No Change (increases in metabolic activity)	ADAS-Cog	Fornix	3-3.5V, 0.09ms pulse width at 130Hz	Testing before and after 12 months of continuous stimulation	[15] [103]

structural volume of MTL structures)							
2010	2	No Change	Standardized Tests – objective Hopkins Verbal Learning Test—Revised, and the Brief Visuospatial Memory Test—Revised and Memory Assessment Clinic Self- Rating Scale	Hippocampus	0.5V, 0.09ms pulse width at 185Hz	3-month baseline period after implantation with no stimulation, then stimulator on/off three months	[109]
2011	5	Neutral/Impairment	Verbal and Visuospatial Supraspan RAVLT RVDT	HC and Amygdala	<2V, 0.45ms pulse width at 130 Hz	The patients were followed up between 12 and 74 months after continuous stimulation. Reducing stimulation intensity reduced impairments.	[110]
2011	10	Improvement (Complex figure) Impairment (verbal with left stimulation)	Many Standardized Tests, including RAVLT, RVL, CSRT Complex figure test,	HC and Amygdala	1-2.5V, 0.45ms pulse width at 130Hz Voltage	Standardized tests were delivered after the first six months of continuous stimulation.	[111]
2012	9	Improvement (in delayed verbal memory)	(IQ, MMSE), information processing (digit forward and backward, Trail A, and Digit Symbol), or executive function (Trail B and WCST)	Anterior Thalamic Nucleus	1.5-3.1V, 0.09-0.15ms pulse width at 100-185Hz	Testing before and after 12 months of continuous stimulation. Some participants had minor changes in their medications during this period.	[107]
2015	6	Stable/impairment	Cognitive subscale of the ADAS-cog	NBM	2-4.2V at 0.09-0.15ms pulse width at 10-20Hz	Four-week double-blind, sham stimulation period, followed by a subsequent 11-month stimulation period.	[105]
2015	2	Stable	ADAS-cog	NBM	2-4.2V at 0.09-0.15ms pulse width at 10-20Hz	Improvement in one, stable in the other	[106]
2016	42	No Change	ADAS-Cog 13, CDR-SB	Fornix	3-3.5V at 0.09-0.15ms pulse width at 10-20Hz	Half assigned to stimulation starting right away and a half to stimulation starting after one year. Tested at baseline, at 6 and 12 months on these and other tests (not presented). No change in the behavioural outcome but tolerated with possible benefit for those >65. Glucose metabolism also increased at six months	[112]
2018	42	No Change	ADAS-Cog 13, CDR-SB, CVLT, NPI	Fornix	3-3.5V at 0.09-0.15ms pulse width at 10-20Hz	Follow up from the previous study after two years of stimulation. Half assigned to stimulation starting right away and a half to stimulation starting after one year. No differences between early-onset and later and any potential benefit for those >=65.	[113]

Conditional Open Loop

When discussing memory frameworks, the hippocampus has a role during encoding, consolidation and retrieval. In a behavioural task in which memory is tested, these same stages exist. The encoding refers to the original presentation of a stimulus that allows for the formation of memory or representation of this stimulus that outlasts its initial presentation. The maintenance or consolidation phase is where such a stimulus is transformed for longer preservation. Finally, the maintenance retrieval stage is when the previously encoded stimulus is recalled. Those MTL structures involved in this process can be stimulated at any time during the behavioural task. Conditional open-loop DBS relies on stimulation agnostic to the underlying neural activity but present during behaviorally relevant stages. Studies implementing this idea are summarized in Table 2.3.

Individuals with epilepsy are critical for the development of such technologies. As part of the clinical treatment, individuals with epilepsy undergo intracranial implants to localize their seizure foci[114]. This population is ideal for conditional open-loop investigations for two reasons as previously described but laid out here:

- 1) Individuals with epilepsy can suffer from memory and cognitive deficits[61].
- 2) A large portion of those who do not respond to medication have TLE[115]. Therefore, the electrodes are often implanted in MTL structures.

One study that demonstrated success used high-frequency stimulation to the hippocampal or entorhinal region in an intermittent fashion (5 seconds on, 5 seconds off) but only during the encoding phase of a spatial navigation task. When comparing hippocampal and entorhinal cortex(EC) stimulation, only EC elicited improvement[12]. However, a later study refuted these claims, demonstrating that both hippocampal and parahippocampal stimulation during the encoding phase of a spatial navigation task and a verbal memory task significantly degraded memory performance[25]. In support of that follow-up, many other conditional open-loop stimulations of the hippocampal and adjacent cortices have demonstrated a significant degradation in memory function over a broad spectrum of memory types[24], [25], [27]–[30], [116], [117]. Recently, proximity to the white matter has been proposed as one reason for such mixed results[118], [119].

The study where DBS improved memory also increased theta-band (typically 3-8Hz) power in the hippocampus[12]. Theta's role in memory is not a new one. Long-term potentiation (a long-lasting strengthening of synapses following specific activity patterns and a form of plasticity) is believed to play a major role in effectively storing and retrieving memories[83]. It is thought that theta-burst stimulation mimics in vivo firing in the hippocampus and is therefore effective in inducing LTP[120]. In animal studies, in support of this mechanism, stimulating at specific times during endogenous theta oscillations' troughs and peaks can produce LTP and LTD, respectively[121]–[124]. Thus, theta-burst stimulation may be a powerful tool to modulate hippocampal plasticity and thus modulate memory.

The studies that have used conditional open-loop theta-burst stimulation(TBS) in humans have found success when stimulating the entorhinal cortex[125], the amygdala[126], and fornix[14]. Recently, TBS has been used to demonstrate connectivity and entrainment of theta rhythms across the brain[127]. To date, this pattern has not been used to stimulate the human hippocampus. Therefore, there is potential for such a pattern to be used successfully in the hippocampus. Even with the implementation of this protocol, there are still limitations of these conditional open-loop approaches. Primarily, they have been run in individuals with epilepsy, so translation to other diseases remains a question.

Additionally, by the very nature of being conditional on stimulus presentation or stage of the behavioural task, the presentation must be completed in a controlled environment. Translating this to a natural world is easy with open-loop stimulation. Clearly, Conditional Open Loop stimulation research relies on knowing when a behavioural stimulus will be presented. Therefore, the controlled setting of knowing exactly when a stimulus will be presented does not easily translate to the natural world.

Table 2.3| Conditional Open Loop Studies

This table provides a summary of all the conditional open-loop studies discussed in this chapter, providing an overview of the methods implemented in each study, along with insights into putative mechanisms of action (as suggested by the authors of the respective studies). Theta burst stimulation (TBS), high-frequency stimulation (HF), low-frequency stimulation (LF), Mesial Temporal Lobe (MTL), Hippocampus (HC), Entorhinal cortex (EC), Rey Auditory-Verbal Learning Task(RAVLT), Parahippocampal Gyrus (PHG), Posterior Cingulate Cortex (PCC), Dorsolateral Prefrontal Cortex (DL-PFC), Temporal cortex (TC), Inter-trial interval (ITI), Superior Frontal Gyrus(SFG) Also used in [64].

Year	N	Stim Type	Memory-Related Outcome	Memory Type	Stimulation Location	Stimulation Parameters	Stimulation Period	Stimulation Protocol	Putative Mechanism of Action	Ref
1985	3	HF	Impairment	Recognition (paired associate words)	MTL Structures	<2mA, 0.1ms pulse width at 51 and 30 Hz	Encoding	Stimulation, delivered during list of paired item presentation.	Impairment of memory due to the spread of after discharges from stimulation	[28]
1985	4	Single Pulse	Impairment	Recognition (complex scenes)	MTL Structures	<1.5mA, 0.1ms pulse width (during image presentation)	Encoding, Retrieval Encoding + Retrieval	Stimulation was delivered for each stimulus presentation.	Stimulation-induced impairment was rescued with a delay, suggesting stimulation impairs the memory trace consolidation.	[27]
2004	5	HF	Impairment	Recognition (faces, words and objects)	HC	1.9-5mA with 1 ms pulse width at 50 Hz	Encoding	Electrical stimulation was alternated based on block and delivered throughout visual stimulus presentation (1.2 seconds)	HF stimulation perhaps acts as a functional lesion. Laterality of stimulation is evident, with left stimulation impairing words, right impairing faces.	[29]

2010	12	Pulse	Impairment	Recognition (faces, words, objects, geometric shapes)	HC	4-6mA, monophasic pulse width 1ms	Encoding, Retrieval, Encoding + Retrieval	Stimulation locked to variable delays with stimulus presentation and varying targets.	Unilateral stimulation of the hippocampus failed to impair memory, whereas bilateral impaired memory. Thus, hippocampi can act independently, and memory formation/retrieval can only be disrupted with bilateral stimulation.	[24]
2012	7	HF	Improvement	Visuospatial	HC and EC	1-2 mA, pulse width 0.3ms at 50 Hz for 5 seconds on 5 seconds off during trials.	During all phases	Stimulation was delivered during a spatial navigation task in half the trials. The shorter the subsequent path to the previously navigated locations, the better the spatial memory.	EC stimulation improved spatial memory performance, perhaps due to enhanced theta phase resetting leading to ideal conditions for LTP	[12]
2013	11	HF	In-phase stim: Improvement, out-of-phase stim: Impairment	Word recall	HC/ Rhinal	0.01mA sine wave at 40Hz	Non-stop during encoding, distraction/ delay and recall phases	Stimulation was delivered to both the hippocampus and the rhinal cortex simultaneously, either in-phase or out-of-phase, or not delivered at all.	Stimulation may entrain synchronization of gamma activity between rhinal cortex and hippocampus which has been correlated with memory formation either through promotion of neuronal communication or facilitation of synaptic plasticity.	[13].
2015	4	TBS	Improvement	Visuo- spatial	Fornix	7mA, pulse width 0.1ms with 5 bursts a second on for 100ms at 200Hz	Continuous across entire testing period	Three tasks with 50% stimulation in each task: Verbal memory (RAVLT), visual spatial (Georgia Complex Figure Test) and visual confrontational naming (Boston Naming Task)	Theta burst replicates naturally occurring firing patterns in hippocampus	[14]
2016	5	HF	Impairment	Word recall	HC and EC	<6mA, pulse width 0.3ms at 50 Hz for 5 seconds on 5 seconds off during trials.	Encoding, Distractor Or Recall	Stimulation was delivered at onset of stimulus presentation for the respective period of the trial	Impairment across all, but significant in distractor period. Stimulation may alter circuitry through membrane potential alterations and mimic a forgetting cue.	[30]
2016	49	HF	Impairment	Word recall and visual spatial	HC and EC	0.5-1.5 mA, pulse width 0.3ms at 50 Hz for 5 seconds of presentation	Encoding	Stimulation was delivered either during 5 seconds of encoding period of placement of object in virtual arena (Morris water maze) or lists of words	Impairment in both verbal and spatial tasks was elicited regardless of hemisphere and only trended in improvement in parahippocampal stimulation. Suggests MTL structure involvement in encoding.	[25]
2017	102 (r)	HF	Improvement based on encoding state	Word recall	HC, EC PHG, Perirhinal DL-PFC	0.5-1.5 mA, pulse width 0.3ms at 50 Hz for 5 seconds of presentation	Encoding	iEEG data from 102 patients was used to develop a model capable of differentiating good vs. bad encoding states. 32 patients were then tested	In general, stimulation impaired memory. However, post-hoc analysis showed that stimulation during the trials that were subsequently marked as being "bad encoding states" actually improved memory.	[128].

	36 (s)							with stimulation, which was delivered randomly 200ms prior and lasting for 4.6 seconds extending until after second word of the pair disappeared.		
2017	13	TBS	Improvement	Recognition (people)	HC and EC	0.05mA, 5 bursts a second, 4 pulses per burst at 0.2ms pulse width, delivered at 100Hz frequency	One second 2.2-2.7 seconds prior to picture onset in encoding	Stimulation was delivered on 50% of the images and the memory of these images was compared with those that were not stimulated.	Improvement only with right entorhinal cortex angular bundle suggesting laterality. Theta burst stimulation may be eliciting LTP like protocols suggesting temporal and spatial specificity. Specifically, white matter stimulation may excite downstream regions	[125]
2018	7	HF	No Change	Associative object and word	EC	0.1 mA, pulse width 0.3ms at 50 Hz for 15 seconds on 15 seconds off	Encoding	Stimulation was delivered during 5-minute encoding period in a 15 second, on-off cycle. During this period, participants learned noun-colour associations that were later tested.	While EC stimulation led to more positive deflections of ERPs in the anterior hippocampus, no behavioural effects of the stimulation were seen, perhaps due to the low stimulation intensities.	[129]
2018	22	HF	Improvement with lateral TC stimulation	Word recall	HC, PHC, Neocortex, PFC, and Lateral TC	0.5-1.5 mA, pulse width 0.3ms at 50 Hz for 5 seconds of stimulation	Encoding	Stimulation applied to 50% of words 200ms prior to word onset and lasted for 4.6 seconds extending until after second word of the pair disappeared.	Only lateral temporal cortex stimulation improved behavioural performance in the task, and also increased high gamma power as a correlate of memory. Full mechanism needs to be explored further. There may also be an underlying modulation of attention or perception.	[116], [117]
2018	4	TBS	Impairment	Spatio-temporal	Customized per subject based on network activity	4-6mA, 4 bursts a second, 3 pulses per burst at 0.2ms pulse width, delivered at 50Hz frequency	2 seconds prior to retrieval (delay/ ITI)	Two target stimulation nodes that exhibited strong coupling for spatial vs. temporal memory were identified using iEEG data from a spatiotemporal memory. TBS stimulation was delivered in a subsequent session to these target nodes with a fixed phase-lag (0° or 180°), in a similar spatiotemporal memory task.	Only spatial memory was impaired. This impairment was accompanied with theta decoupling of the spatial retrieval network.	[130]
2018	14	TBS	Improvement	Recognition	Amygdala	0.5mA, 8 trains of 4 pulses per burst at 0.2ms pulse width, delivered at 50Hz frequency	1 second at offset of image (delay/ITI)	Theta burst stimulation at the end of the encoding period (image offset). Memory was tested immediately after and following a 1-day delay.	Increased memory performance a day later and increased theta gamma interactions. Perhaps through glutamatergic release from amygdala and slower robust molecular changes and plasticity that can only be seen with a long delay.	[126].
2018	7	HF	No Change	Associative	EC	0.1mA, pulse width 0.3ms, 50 Hz stimulation, 15 s on	Encoding	During encoding periods 15 seconds on 15 seconds off	Low amplitude more physiologically occurring, but no memory change for any stimulation. Was a change in ERP in the hippocampus in stimulated vs non-stimulated items.	[129]

2019	6	HF	Improvement	Associative word recall	HC	0.5-1.5 mA, pulse width 0.3ms at 50 Hz for 5 seconds of stimulation	Encoding + ITI (not distractor)	Stimulation was applied during 5 seconds of encoding and was randomly assigned to blocks of stimulation	Improvement in memory was dependent on task. Theta power increased in lateral middle temporal cortex in stimulation trials that were later remembered. Synchronous membrane fluctuations and enhanced long-range communication facilitated by stimulation may enhance recollection and theta power across network.	[26]
2019	17	HF	Impairment	Free recall	PCC	<7.5mA, pulse width 0.2ms, at 100Hz for 25 seconds	Encoding	Stimulation applied during the entire encoding phase during 50% of the list	Stimulation impaired memory and resulted in increased gamma and decreased theta. However, when looking at SME reduction in sme that correlated with memory disruption	[131]
2019	3	HF	Improvement /impairment	Associative button and image	Caudate	2mA, pulse width 0.2ms, at 200Hz for 1 second	Retrieval/ Feedback	Stimulation during half the images during the feedback, if correctly learned button associated with the image.	Caudate stimulation resulted in improvement and beta increase in DL-PFC. Putamen stimulation impaired learning	[132]
2019	3	LF	No Change	Working Memory	SFG	2 mA, pulse width 0.4ms at endogenous frequency (10, 9 and 5 Hz) for 5 seconds or all session of stimulation	Encoding	Stimulation determined based on the peak in power spectra of baseline session	Reduction in reaction times but no modulation changes.	[133]
2021	22	HF and TBS	Improvement	Person Recognition , Object Recognition , and Face-Name Associative Memory	EC white and grey	Macro: 0.4mA-5.9mA, pulse width 0.3ms, 50Hz Micro: 0.150 mA, 5 bursts per second, of 4 pulses per burst at 0.2ms pulse width, delivered at 100Hz frequency	Encoding	Stimulation delivered in the period before stimulus presented	Stimulation of white matter adjacent to right EC showed improvement, while grey matter and left EC showed no change.	[118]

2.3.2 Closing the Loop

Closed-loop simulation presents a step in the right direction for translating research to home and community settings since knowledge of external events would not be required. Closed-loop systems rely on feedback to adjust the input and regulate the output. By taking into account the underlying neural activity to guide the timing of stimulation, the effectiveness of stimulation on memory outcomes may be improved. Two major studies exist to date that have employed closed-loop stimulation.

iEEG electrodes that can be used for DBS can also be used to record neural activity. Subsequent memory effects (SME) demonstrate that some frequencies can be correlated with memory formation. For example, a decrease in theta power and a simultaneous increase of higher frequency gamma power before stimulus onset represents a better ‘brain state’ for encoding[134]–[139]. It is believed that such changes reflect an increase in asynchronous neuronal spiking and are thus reflective of increased cortical excitability[140]–[142].

Alternatively, single-unit neuronal firing correlates with memory formation in SME[143]. Two promising closed-loop studies have used these concepts on the ongoing 1) frequency of activity and 2) neuronal firing rates.

Ezzyat et al. (2017) found that in open-loop stimulation, they could classify above chance when an item would be remembered using frequency band powers as features to a classifier[128]. They found that with open-loop stimulation, overall memory was degraded by stimulation. However, when classifying items in what they called a bad encoding state were more likely to be remembered when stimulated. A subsequent follow-up study found that closing the loop based on these features, and stimulating the lateral temporal cortex improved memory performance[144].

Another recent closed-loop stimulation study looked at more specific stimulation within the hippocampus. As previously discussed, the hippocampal subfields, CA1 and CA3, are in direct communication where CA3 can drive activity in CA1 along the trisynaptic pathway (Figure 2.3). Recording with microelectrodes, Berger et al. could find single-unit firing patterns to remembered and forgotten items. Almost a decade ago, they developed a multi-input multi-

output (MIMO) system to predict output firing patterns in CA1 using input firing patterns from CA3 in rats performing a spatial memory task[145], [146]. Through detecting when a weak input/forgotten item was encoded, they could effectively stimulate the strong pattern to improve performance. Such findings were replicated in nonhuman primates (NHPs) using spatial and recognition memory tasks[18] and even recently performed in humans[147].

Both these studies represent inspiring progress in the field of DBS. However, in both of these studies, stimulation is only delivered during the behavioural task's encoding phase. Timing and pattern for delivery of stimulation can be essential to the behavioural outcome. Translation out of the clinic again is difficult as one does not know precisely when a person will be presented with an encoding stimulus. Therefore, a natural timing for stimulation delivery is critical for future DBS implementation and understanding of memory.

2.4 Potential Natural Timing for Stimulation

2.4.1 Eye Movements and Memory

Given the previous result on the importance of timing to stimulation for memory improvement, it is critical to find a naturally occurring timing mechanism translatable to the real world. One potential temporal window into memory processing might be eye movements[148]. The memory test of an image being remembered in infants[149] and non-human primates[150] relies purely on spending less time on a subsequent viewing[149], [150].

In the context of memory, Noton and Stark proposed a Scanpath theory[151]. Specifically, they suggested that eye movements follow a similar sequential path as the originally encoded memory trace in the repetition of a stimulus. Accordingly, subsequent viewing would facilitate comparing previously-stored memories with incoming perceptual input to support retrieval. In support of this, it has been shown that eye movements along the scanpath, especially at the beginning of the task, are repeated in subsequent viewing[152], [153], and this correlates in reduced search time in young adults with better memory performance[152].

In the scanpath hypothesis, there is some evidence that reinstatement of the previous path can support hippocampal circuitry and the encoding/retrieval process. For example, the number of fixations is correlated with something being subsequently remembered[148], [154]. The duration of fixations can also be important for memory formation[155]. Even how stimuli are viewed can be important for memory formation. Specifically, if natural viewing is allowed, the stimulus will be more strongly remembered than if viewing is restricted[153] or even yoked to another viewing sequence[156].

It has been suggested that eye movements are involved in two major proposed neurocomputational processes involved in memory storage, through pattern separation[148] and recently in pattern completion[157]. Encoding a complete stimulus by storing its elements distinctly is known as “pattern separation.” The retrieval process by which partial fragments or cues can recall a full memory is known as “pattern completion.” It is believed that these processes can be teased apart through behavioural responses to recognition tasks[158]. Specifically, lure targets have been used that look similar to an original, presented item. If it is correctly identified as new, pattern separation is thought to have occurred. If it is a false alarm and identified as old, pattern completion may be involved.

For pattern separation, it has been suggested that if pattern completion were involved as a retrieval-related function, there would be no difference between the number of encoding fixations and the behavioural outcome. In support of pattern separation, the number of fixations does correlate with behavioural outcomes[148], [154]. Alternatively, recently it has also been shown that the more a fixation path follows the original encoded path, the more likely an item is to be falsely remembered[157]. Therefore, it seems that eye movement can be involved in memory processes and its relational component (for reviews, see[159], [160]).

Interestingly it is not only eye movements but also the pupil diameter that can predict memory and pattern separation[154], [161], [162]. The pupil diameter can respond purely to the stimulus presentation. As we describe these processes about eye movement and behavioural responses, it is not surprising to see that they are also evident in the hippocampus as described above, with pattern completion ascribed to CA3[68], [72] and pattern separation primarily in the dentate gyrus and CA1[163].

2.4.2 MTL and Oculomotor Connectivity

The concept of the hippocampus and eye movements being involved in a similar behavioural process may be surprising at first. Still, when delving deeper, the relationship does appear grounded in brain connectivity. The hippocampus in one model sits at the top of the visual hierarchy[164]. Recent models show strong indirect connections between the oculomotor and mnemonic systems[165]. Specifically, brain areas necessary for the cognitive control of eye movements, such as the dorsolateral prefrontal cortex and frontal eye fields, are connected to the hippocampus. All hippocampal subregions except the dentate gyrus have a disynaptic connection to either the frontal eye fields or deep layers of the superior colliculus, areas critical for eye movement initiation.

In addition to these connections demonstrated through structural imaging, evidence also exists for functional connectivity. Specifically, the number of fixations correlates with hippocampal activation[166]. Even if there is no conscious recognition, hippocampal activity predicts more extended subsequent viewing of a stimulus[167]. Hippocampal activation can even be connected to eye movement overlap between test and study[168].

Even without such imaging, impairments in memory can be correlated to deficits in eye movements. For example, fractional anisotropy reflects diffusion, with higher values reflecting higher degrees of organization and connectivity. More symptoms and lower fractional anisotropy are associated with smaller amounts of saccades in concussion-related syndromes in a task designed to maximize total saccades[169]. Amnesiac patients with MTL damage also demonstrate different viewing patterns than healthy controls[170], [171]. Specifically, they spend less time viewing manipulated regions in the absence of explicit awareness of the manipulation[170] and spend less time viewing correctly matched paired stimuli than healthy matched controls[171]. Similarly, cumulative viewing time over multiple exposures to a trigger can be predictive of memory formation, yet this effect does not persist in an amnesiac patient with decreased hippocampal volume[172]. Even visual neglect, the inability to visually perceive one side of the body, might be connected to MTL damage[173].

It is evident that eye movements and memory are connected in behavioural analysis. These systems are interconnected based on white matter connectivity, and when one system is impaired, the other system also has deficiencies. Interestingly, we can also connect stimulation to the connectivity of the two structures. Electrical stimulation can indicate connectivity based on the resulting response in other recording electrodes[174]–[178]. These evoked responses are known as corticocortical evoked potentials (CCEP). In non-human primates, stimulation in the MTL post saccade resulted in an enhanced amplitude of the CCEP compared to stimulation agnostic to a saccade[179]. These results raise the question of how the timing of eye movements can be used to guide stimulation.

2.4.3 Phase Reset: Event-Related Potentials from Eye movements and Visual Presentation

Conditional open loop and closed loop studies to date rely on stimulus presentation to time stimulation. Closed-loop stimulation depends on SME and the difference in neural activity between remembered and forgotten items. Specific features used to understand when an item will be remembered rely on aspects of the ongoing signal such as its phase, frequency or power. One way to investigate these features of the electrophysiological signal involves aligning multiple trials of stimulus onset and averaging to obtain the event-related potential (ERP). The event response is evident to each stimulus, but such averaging increases the signal-to-noise ratio for subsequent analysis. The features of the signal and resulting ERP have been proposed to have a functional connection to the underlying neural activity[180], as suggested in Figure 2.6.

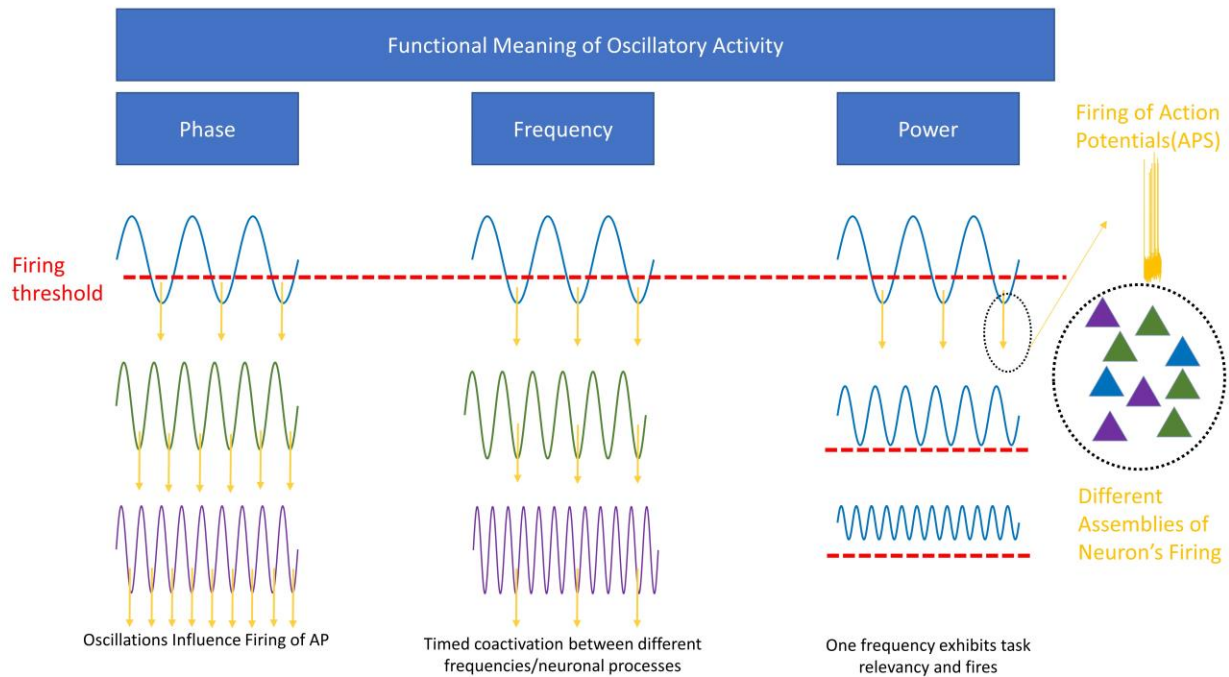


Figure 2.6 | Oscillations and proposed functionality: Neurons can fire to specific phases of frequency, evidenced by firing closer to the trough of the ongoing oscillation of various frequencies. Coupling of activation between different frequencies of activity can also be recorded where firing/activation occurs at similar times and phases across different assemblies. Finally, the relevance of an oscillation power to a specific task can be recorded whereby one oscillation may have increased power and firing while other frequencies may not be engaged. This figure is used in [181] inspiration from Klimesch et al. [182].

ERPs caused by a phase reset provide a mechanism for synchronizing neural activity[183]–[185]. Phase resetting by definition is the re-alignment of an ongoing oscillation to a particular reference point, either through internal or external means. A phase reset can align ongoing activity to a specific temporal reference. This enables periodic stimulus to control a neuronal oscillator’s phase, aligning it appropriately[185]. Stimuli can subsequently arrive at the appropriate phase to induce plasticity by the increased synchronization.

A theta phase reset is a naturally occurring phenomenon that occurs in animals through tail pinching[122], afferent stimulation[186]–[188], and light[189]. Such a reset provides an optimal LTP window, a mechanism known to be involved in memory[189]. For example, stimulation during the peak of theta produced LTP in rats[121], [122], [189]. To investigate such a phase reset in humans, it is critical to look at the neural activity's underlying features that contribute to

the electrophysiological response of the ERP (e.g., underlying frequency content in power, phase and correlations between regions).

Since these spectral features (frequency, phase, power) are so relevant for communication, it is not surprising that SME research has investigated these features of the ongoing oscillation and ERP to analyze their connections to memory formation. Research has been done on visual stimulus presentation (for words[137], [190], [191], Sternberg probes[192], [193], complex visuals[194]) and eye movements[195], [196] to predict when a stimulus might be remembered. The difference in the amplitude of the recorded response, the phase and the power of ongoing activity in MTL structures have all been correlated to memory formation.

The critical key for timing is to determine which stimulus, image onset or eye movement, results in the clocking mechanism of a phase reset. To determine which stimulus results in a phase reset, it has been proposed that for a true phase reset, the evoked response generation would result from phase synchronization with no power change[180]. However, both image onset[197] and eye movements[198], [199] have been proposed to be involved in this mechanism.

Both of these responses also produce an ERP with a corresponding peak and trough. In fact, in animals, stimulation at the corresponding trough after a phase reset resulted in the strengthening of the response, while stimulation of the trough resulted in weakening[189]. One key opportunity is to determine the mechanism of generation of eye movement compared to image onset. Once a true phase reset mechanism is established, the subsequent peak and trough timing can be extracted from the ERP.

2.4.4 SPEAR Model

An ERP to a visual stimulus typically results in a prominent peak and trough. Timing specificity of the neural activity raises another question about the importance of the resulting theta phase reset and its subsequent peak and trough. In rodents, hippocampal neurons tend to oscillate in tandem between excitatory and inhibitory states at a rate of 3-8 cycles/second (theta rhythm)[200]. Stimulating neurons during the trough of theta strengthens their connections expectedly, the same stimulation applied during the peak weakens their connections[121], [122], [201]. This well-replicated physiological effect also influences rodent memory, with

manipulations at peak and trough differentially influencing retrieval and learning[202]. These findings motivated the powerful idea that theta rhythms determine how we use memory, preparing us to form memories during its troughs and retrieve memories during its peaks, now known as Separate Phases of Encoding And Retrieval (SPEAR)[203]–[205].

The SPEAR model presents key mechanisms that optimize the hippocampus to encode memories during the trough of theta and retrieve them during the peak¹[203]–[205]. The first involves the pathways through which information flows in the hippocampus. Information about the external environment arises from the entorhinal cortex, the primary cortical input to the hippocampus. By contrast, internally reactivated memories are thought to emerge from the CA3 subfield of the hippocampus, supported by its dense recurrent connections. The SPEAR model proposes that entorhinal input is strongest during the trough of theta, biasing area CA1 to process external events, but that CA3 input is strongest during the peak, biasing area CA1 to process retrieved memories.

The second mechanism involves synaptic plasticity—namely, long-term potentiation (LTP)—thought to underly memory formation. According to the SPEAR model, LTP is facilitated during the trough of theta, when synaptic input from the entorhinal cortex is strongest. The resulting postsynaptic activity in CA1 is associated with (weaker) presynaptic activity in CA3 to support encoding. LTP is proposed to be comparatively weaker during the peak of theta to prevent new material encoding during retrieval.

Animal research provides clear support for many aspects of this proposal. It has been demonstrated that neurons in the CA1 subfield fire at different theta phases for novel(encoding) vs repeated(retrieval) stimuli[206] and that theta phase-dependent optogenetic inhibition in CA1 can enhance behavioural performance based on timing its delivery to appropriate encoding or retrieval segment in a maze[202]. The trough of theta from fissure is also in sync with entorhinal cortex activation of the dentate gyrus[207], [208]. At the same time, CA1 and CA3 are most

¹ We will be using orientation from the hippocampal fissure which is 180 degrees out of phase when recording from CA1 and stratum radiatum. Therefore, peak in some studies from this reference are actually trough[389]

active during the ascending phase of theta in both firing and theta gamma interactions[209]–[211]. Consistent with phase dependency, contingent theta phase stimulation modulates synaptic plasticity. Applying electrical stimulation to CA1 on the trough of theta induces LTP[121]–[123], [189], but when the equivalent stimulation is applied on the peak, it causes depotentiation (LTD) ;[121]–[123], [212].

Such phase predictions have only recently begun to be tested more directly in humans. Kerrén et al. (2018) used surface EEG to demonstrate that classifier evidence for retrieved content oscillates at a theta rhythm. Moreover, periods of especially strong retrieval evidence were preceded by high theta phase consistency in the temporal lobe. This work suggests an optimal theta phase for memory retrieval and provides preliminary evidence that hippocampal theta could be involved in these dynamics. Kragel et al. (2020) used intracranial recordings to more directly assess hippocampal theta[196]. They inferred periods of encoding and retrieval from memory-guided eye movements. Theta phase coherence increased before fixations on previously relevant locations (perhaps reflecting retrieval) and after fixating on new elements (perhaps reflecting encoding). Importantly, phase coherence was concentrated at opposing phases for these different brain states of encoding and retrieval as separated by eye movements. Thus, while less direct than the causal manipulations used in rodents, emerging evidence suggests that humans' memory formation may also be related to specific hippocampal theta phases.

These causal manipulations have yet to be used in humans. On the surface, it would seem feasible also to stimulate the hippocampi of people at particular theta phases and determine how this influences their memory. However, when compared to rodents, human theta is comparatively evanescent; during navigation, rodent theta is sustained and dominates hippocampal recordings[200], but under similar conditions, it only occurs in brief bouts in humans and monkeys[213]–[215].

Therefore, we can utilize, instead of ongoing theta, the theta phase reset. One innovative example, McCartney et al. (2004), leveraged the principle that task-relevant events can reset the phase of hippocampal theta to time their electrical stimulation[189]. Specifically, they measured the average time to theta peak and trough following the presentation of a cue in a memory task in rats. Following these calibration sessions, they applied high-frequency stimulation at these

estimated peak or trough times to demonstrate that LTP was only elicited in response to trough stimulation. Together, this body of work strongly suggests that the hippocampus is primed to learn during theta peaks. Eye movements or image onset may produce a phase reset and a subsequent peak/trough to deliver stimulation. Such a phase reset and resulting ERP presents an opportunity for causal exploration of the SPEAR model in humans.

2.5 Hypothesis and Objectives

To understand the relationship of the SPEAR model to human memory, this PhD thesis seeks to investigate the temporal organization of human memory by **studying the effects of stimulation timing on memory formation in individuals with epilepsy undergoing invasive electrical recordings. Specifically, the aims are:**

1. Determine optimal stimulation timing during a visual memory task based on timings obtained from visual ERP responses that demonstrate a theta phase reset.
2. Determine if this theta phase reset is supported through single-unit recording, and
3. Determine effects of phase-based stimulation timing on behavioural memory performance.

3 Visual Phase Reset for Optimal Stimulation Timing

This chapter has adapted the material from a previously published manuscript in *Cerebral Cortex*[216] and is reproduced with permission.

Katz, C. N.*, Patel, K.*, Talakoub, O., Groppe, D., Hoffman, K. L., & Valiante, T. A. (2020). Differential Generation of Saccade, Fixation, and Image-Onset Event-Related Potentials in the Human Mesial Temporal Lobe. *Cerebral Cortex*, <https://doi.org/10.1101/442855>. <https://doi.org/10.1093/cercor/bhaa132>

3.1 Introduction

The electrophysiological responses of mesial temporal lobe (MTL) structures, known for their critical role in memory, have been characterized using a variety of behavioural paradigms and described according to their temporal relationship to stimulus onset (i.e. image-onset, word presentation, etc.). Neural responses following image presentation have been reliably used to study memory processes[190]–[192], [194], [217]–[219], whereas, despite a rich literature linking eye movements to memory (for review see [220]), very few have investigated electrophysiological responses of human MTL structures to eye movements[199], [221]. At first glance, image-onset and saccadic eye movements both present salient information to visual centers, suggesting that subsequent processing would be similar, as would be the electrophysiological responses to them. Conversely, if such responses differ, it would suggest that their neural correlates differ, and that tasks/analyses that preferentially favor analyzing responses to one or the other are capturing distinct visual and likely mnemonic processes.

Arguments can be made to support or refute why MTL electrophysiological responses to image onset and saccadic eye movements might appear similar. Intuitively, since the hippocampus is a multimodal integrator far removed from primary visual cortex, it may be agnostic as to how visual information arrives[222]. In this context any new retinal information, independent of its generation, would result in the same electrophysiological response. The

literature however suggests visual and oculomotor responses are likely to be different. For example, MTL responses to the presentation of images, which are consistently used for investigations in word paradigms[190], [191], Sternberg probes[192], and complex visuals[194], are usually long latency responses with large amplitudes[194], [197], [221]. These MTL responses can be looked at through recognition, working memory or even recall tasks (presentation of first stimulus), with focus on the response to presentation of the visual stimulus. On the other hand, eye-movement related responses in the MTL tend to have a shorter latency and lower amplitude[221]. In line with these findings are those of Bartlett et al. who specifically compared the responses within macaque superior temporal sulcus (a region analogous to the human brain region responsible for integrating auditory and visual information[223] to image presentation and eye movements[224]. Their results suggested a clear distinction between image-onset and eye-movement related responses in the time and frequency domain, and as well that the image-onset response can be modulated by succeeding eye movements. The precise origin of eye-movement related ERPs is likely dependent on where recordings have been performed, nevertheless there is indeed support for the concept that they in part represent a corollary discharge. Corollary discharges represent a transformed copy of a motor command signal that informs sensory systems of impending motor activity, thereby distinguishing self-generated changes in sensory signals from the changes generated from the external world[225]. Such a signal can propagate widely throughout the brain, as well as through the ventral visual pathway and temporal lobe structures[226], [227]. If indeed the MTL response to eye movements results in part from a corollary discharge, it would imply a fundamental mechanistic difference in how visual information is processed in mnemonic structures like the human hippocampus. However, it remains an open question whether the human mesial temporal lobe structures respond differently during these two processing conditions (i.e. image presentation and eye movements) – conditions that have substantial effects on memory and the corresponding electrophysiological measurements in the MTL[190], [194], [199], [221], [228], [229].

A variety of invasive and non-invasive electrophysiological recording techniques have been used to study MTL physiology[134], [217], [230]–[233]. Intracranial electroencephalography (iEEG), unlike other recording modalities, provides access to neural activity with high spatial and temporal resolution allowing investigation of electrophysiological

activity in deep structures at ‘fast’ time scales[234]. Such activity can be seen in single trial events or averaged across trials aligned to events/stimuli to obtain event-related potentials (ERPs)[235]. ERPs can be then further decomposed into their respective frequency components, to associate increases/decreases in power/phase clustering to various memory processes[190], [194], [228], [229] and have been used to infer putative neuronal mechanisms like phase-resetting[185], [219], [236], [237]. The study of ERPs has thus contributed significantly to our understanding of MTL function by allowing the attribution of changes in timing, amplitude, and spatial organization of brain related activity to putative cellular mechanisms thought to underlie the generation of such specific electrophysiological signatures[238].

ERPs are widely thought to be generated by either 1) stimulus-specific firing of additional neurons (evoked responses) or 2) post-stimulus phase-alignment of ongoing neural oscillations without additional neuronal firing (phase-reset response)[180], [239], [240]. Broadly speaking, the primary and most basic distinction between these two mechanisms is that evoked responses demonstrate an increase in individual trial power post-stimulus onset, whereas phase-reset responses do not[180]. Identifying which of these putative mechanisms underlies a specific ERP not only characterizes the neuronal response, but also suggest what physiological processes underlie the response. For instance, in the auditory cortex of animals, ERPs arising from somatosensory stimulation appear as a phase-reset, arising from the “modulation”[241] of the timing of neuronal activity within the auditory cortex, without an increase in excitability[242]. This preferential alteration of the timing of neuronal activity through phase-resetting is thought to be important in plasticity mechanisms, and transmission of information within the nervous system[183]–[185]. Conversely, ERPs within the auditory cortex from auditory stimulation appear as an evoked-response, resulting from “driving”[241] increases in neuronal excitability[242]. Therefore, the characterization of ERPs following image presentation and eye movements using this framework, can provide mechanistic insights to MTL electrophysiological responses.

Thus to begin understanding the neural correlates of image onset and eye-movement associated ERPs in humans, MTL responses to image-onset and eye-movements were characterized and compared in epilepsy patients undergoing iEEG investigations using a scene

recognition task previously shown to have mesial temporal lobe dependency[243]. Intertrial phase clustering (ITPC) and spectral power were used to compare MTL electrophysiological responses to saccadic eye movements and image-onset. We demonstrate that the MTL responses following image-onset and saccade-onset events are starkly different with the former being a primarily evoked response showing within-trial power increases and phase clustering in lower frequency bands (delta and low theta) and the latter being best described as a phase-reset in the delta/theta/alpha frequency bands with significant phase clustering in the absence of within-trial power increases. We further demonstrate that saccade associated ERP are initiated with saccade onset and not fixation, suggesting that the ERP associated with saccadic eye movements is initiated before retinal reafference, suggesting it is an internally generated signal like a corollary discharge[221], [227].

3.2 Methods

3.2.1 Method Details

3.2.1.1 Subject Details

This study reports data from 11 subjects (6 females, 36.2 ± 9.7 years of age) with medically refractory epilepsy, who were implanted with subdural surface electrodes and depth macroelectrodes to localize epileptogenic regions (Table 3.1). Electrode locations were selected strictly on clinical grounds. These experiments were performed between 2 and 10 days post-operatively. All research was performed in accordance with protocols approved by the University Health Network Research Ethics Board.

Table 3.1 | Patient Summary Table – Data for each participant is shown in the respective rows. Rows highlighted in black, identify patients who were not analyzed due to insufficient data and poor eye-tracker calibration. HC: hippocampus; PHG: Parahippocampal Gyrus; RAT: Right Anterior Temporal

ID	Sex	Age	Resection	PHG	HC	# Saccades	Median Saccade	Median Fixation	# Blocks Completed

							Duration (ms)	Duration (ms)	
P1 4	F	28	RAT	2	0	12281	16	225	9
P1 5	M	44	RAT	1	2	1909	75	109	2
P1 6	F	39	RAT	2	4	16676	17	151	11
P1 7	F	32	NA	1	2	3177	9	242	2
P1 8	M	28	NA	1	1	17894	9	267	12
P1 9	M	32	NA	4	1	4739	9	501	9
P2 0	M	36	NA	1	2	14508	9	300	12
P2 1	F	25	RAT	2	0	20717	16	217	12
P2 2	M	31	NA	1	2	808	192	108	3
P2 5	F	45	RAT	1	2	16701	9	276	12
P2 6	F	58	NA	2	3	11267	9	259	6

3.2.1.2 Experimental Design

The experimental design of this study is identical to that described previously [199]. A summary is provided here. Participants were seated comfortably in their hospital beds and performed the task on laptop computer. For each trial, an original scene (taken from a large collection of natural scenes including landscapes, wildlife, cityscapes and indoor scenes) was shown at a full resolution of 1280x1024 and alternated with a target-modified scene every 500ms, with a 50ms grey screen separating these images. The target-modified scene was always a modified version of the original scene, in which one object in the scene (here called the ‘target’) was modified in Adobe Photoshop to give the impression that it disappeared. The size, location and content of these targets were modified between different scenes to reduce predictability. Participants were asked to search for the target in each pair of alternating images and could elicit the end of the trial by fixating their eyes on the target for a period of 1000ms. Once they found the target, or after a time limit of 45 seconds, the trial ended with revealing the target by rapidly altering between the two images without the grey screen gap. Trials were presented in blocks of 30, and each participant participated in up to 12 such blocks of data collection. Each scene pair was either novel or repeated once from a previous trial, with equal probability. Between trials in each block, participants were presented with a series of screens asking for verbal responses for the memory of the scenes and targets. Behavioural data from the inter-trial period is not presented or discussed here. An overview of the task and stimuli presentations is presented in Figure 3.1A and B.

3.2.1.3 Eye Tracking Analysis

Eye tracking was performed using the iView RED eye tracking system. The eye tracker was placed at the bottom of the screen, while patients were seated comfortably in their hospital beds, with the screen placed approximately 60cm from their eyes. All participants first underwent a 9-point calibration of the eye tracker system. The eye tracker was connected via a USB cable to the laptop computer on which the behavioral task was presented. It was interfaced using the same software (NBS Presentation) that was used to present the task. Eye tracking data was pre-processed to identify saccade and fixation events using the iView X iTools IDF Event Detector

(SensoMotoric Instruments, Teltow, Brandenburg, Germany). Fixation events were detected by this commercial software using an Identification by Dispersion-Threshold (IDT) algorithm. This algorithm uses two fixed thresholds: a maximum fixation dispersion threshold (100 pixels) and the minimum fixation duration threshold (80ms)[244]. To be considered a fixation, the gaze must stay within the dispersion threshold for at least the specified duration threshold. The end of each fixation event is marked as a saccade event. This saccade and fixation events detected with this algorithm have been shown to be robust for low-sampling eye trackers. In a comparative analysis of 10 eye-tracking algorithms, the IDT algorithm used here was shown to be second closest to human detection for saccade events[245]. A sample of fixations detected is presented in Figure 3.1C.

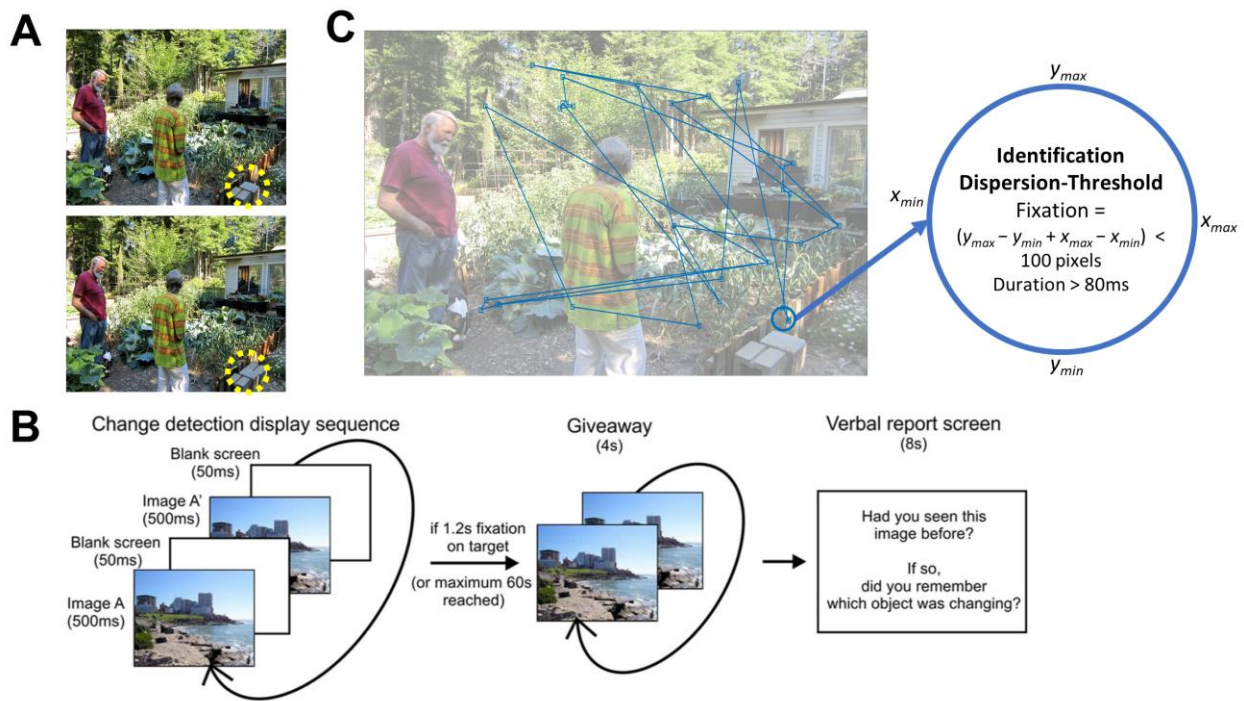


Figure 3.1 | Behavioural task and fixation detection: A) Sample visual stimulus with target objects such as a disappearing brick shown circled in yellow. B) A trial sequence which shows the image switching between the two stimuli for target search. Giveaway is when the target is found, or time has passed, and participants then report on whether or not they have seen image. C) Fixation events from a sample subject. Each fixation event is detected using an algorithm provided by the manufacturer of the eye tracker. As can be seen here a fixation must stay within the 100-pixel dispersion for at least 80ms to be considered a fixation event. The end of a fixation event is considered the start of the subsequent saccade.

3.2.1.4 Neural Recordings

Electrophysiological data presented here were recorded using depth macroelectrodes with four electrical contacts placed to record hippocampal activity. A 4-contact subgaleal electrode was used for ground and reference and was placed over the parietal midline facing away from the brain. Signals were sampled at 5kHz, and hardware filtered from 0.1 to 1kHz, with a NeuroScan SynAmps2 data acquisition system (Compumedics, Charlotte, NC, USA). Neural data was synchronized with eye-tracking data with the use of TTL triggers sent from the laptop computer to the NeuroScan computer. Electrode localization was performed by co-registering pre-op MRI with post-op CT using the iELVIS toolbox[246]. Following localization, the precise location of each of the 4 hippocampal electrodes was determined. Only those labelled as parahippocampal or proper hippocampal, and later verified by a neurosurgeon, were analyzed further. All electrophysiological data was pre-processed by bandpass filtering between 0.5 and 200Hz using second-order Butterworth filter, downsampling to 1kHz, and notch filtering at 30Hz and 60Hz to remove line noise and artifacts. All further analysis was performed using custom-written scripts in MATLAB (The Mathworks Inc, Natick, MA, USA).

3.2.1.5 Data Analysis

3.2.1.5.1 Event-Related Potentials (ERPs)

To obtain ERPs for image-onset events, iEEG data from all trials and all relevant electrodes were aligned to the initial image-onset and trimmed to epochs containing 1.6 seconds of data before and after each event. The ERP for each electrode was then obtained by taking the mean of these image-onset epochs across all trials from all experimental blocks (1 image onset event per trial X 30 trials per blocks X up to 12 blocks per subject = ~360 image onset events for each ERP). Fixation and saccade ERPs were obtained in a similar manner ($\pm 1.6s$ around saccade and/or fixation onset) from the period following image onset, up until the end of the trial (when the target is found or revealed). As such, only saccades and fixations during the active visual search are used for analysis here. It should be noted that the temporal alignment of the ERPs is limited by the sampling frequency of the eye tracker (i.e. 120Hz) and the refresh rate of the display (i.e.

60Hz). This resolution may introduce some temporal jitter into the subsequent analysis, preventing elicitation of higher frequency phase clustering (if such were to exist).

3.2.1.5.2 Alignment of ERPs to fixation or saccade events.

The extremely rapid nature of saccades (median length of 9ms across all subjects) makes it difficult to distinguish between a saccade-aligned ERP and a fixation-aligned ERP (Figure 3.2A). To determine whether the observed saccade-aligned ERPs and fixation-aligned ERPs were distinct events, or the same event viewed from different time points, the saccade-aligned and fixation-aligned ERPs were calculated for varying saccade durations. To do this, saccade and fixation epochs were binned based on the duration of the saccade succeeding the saccade-onset and preceding the fixation-onset. Considering the eye-tracker sampling rate of 120Hz, the first bin was centred at 8ms with a width of 8ms. Succeeding bins were separated by 8ms and had the same width. Saccade lengths greater than 56ms were not analyzed for the sake of this comparison because of the small number of saccades in each succeeding bin. Fixation and saccade-aligned ERPs were then obtained by averaging all the epochs within each bin. These ERPs were then normalized by z-scoring (to control for the varying number of epochs in each bin) and plotted on a contour plot (Figure 3.2C for saccade-aligned ERPs and Figure 3.2D for fixation-aligned ERPs), with varying saccade durations on the y-axis and time relative to saccade-onset (Figure 3.2C) or time relative to fixation-onset (Figure 3.2D) on the x-axis.

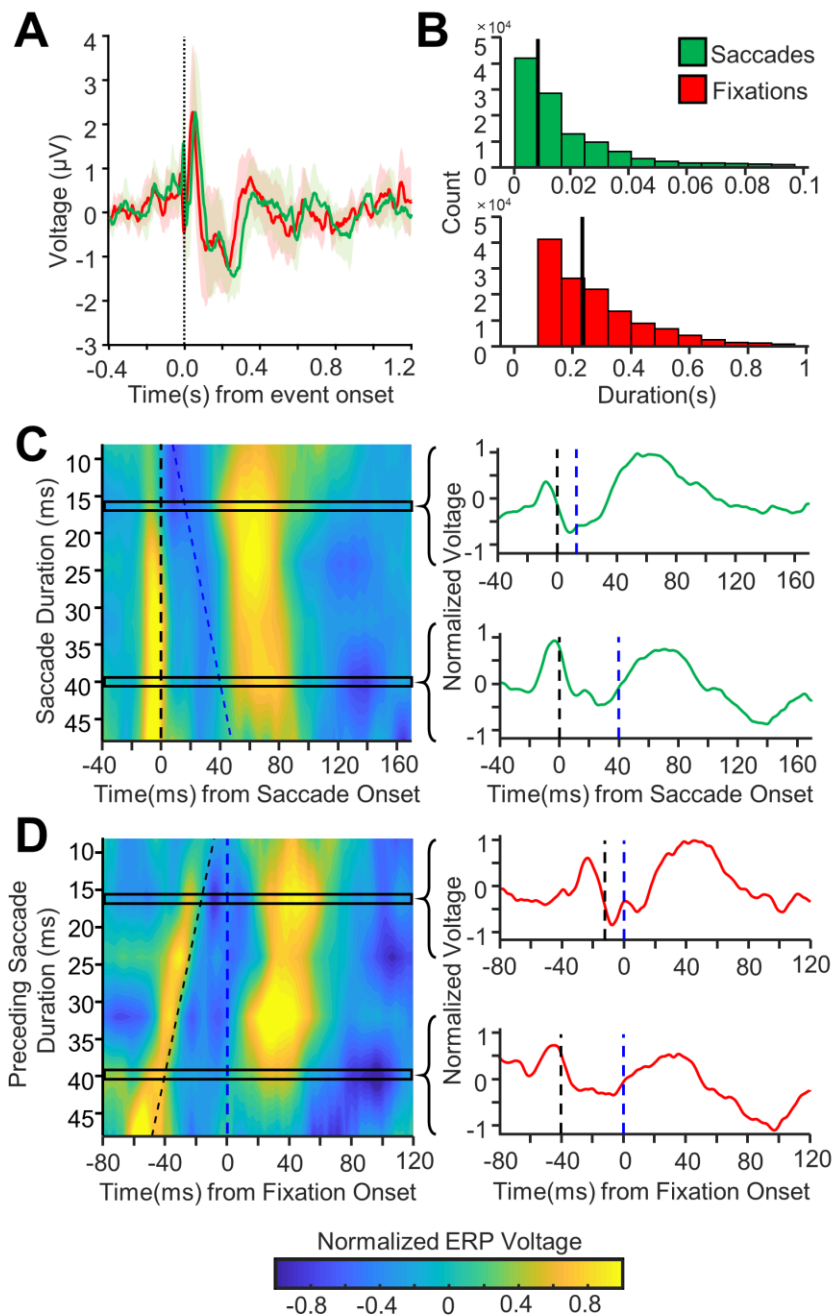


Figure 3.2| Saccade vs. fixation alignment of hippocampal response to eye movements : A) Grand-average Hippocampal ERP aligned to fixation (red) or saccade (green) onset (mean \pm 95% confidence intervals). B) Histogram of fixation and saccade lengths across all patients and trials. The vertical black line marks the median fixation and saccade duration respectively. C) Left: Contour plot showing grand average saccade-aligned ERPs for changing saccade durations (shorter saccade durations towards the top of the graph, longer durations towards the bottom) for all hippocampal electrodes. The x-axis shows time relative to saccade onset. Saccade onset is marked by the dashed black vertical line. Fixation onset is

marked by the dashed blue line. Note that as the saccade duration changes, the response remains aligned to the saccade onset. Each response to saccade duration ERP appears to have a rapid voltage response at saccade onset likely due to extraocular muscle contractions (along the black dotted line), further discussed in the results under ANALYSIS AND REMOVAL OF THE PERI-SACCADIC TRANSIENT. Right: the normalized ERP waveforms for two different rows of the contour plot is shown with the saccade onset marked with a dashed black line and fixation onset marked with the dashed blue line. Note, the saccade ERP is very similar for saccades of different durations across all electrodes. D: Left: As C but for fixation-aligned ERPs. Y-axis shows the duration of saccade preceding the fixation. The x-axis shows time relative to fixation onset. Fixation onset is marked with the dashed blue line, and saccade onset is marked with the dashed black line. Right: the normalized ERP waveforms for two different rows of the contour plot are shown with the saccade and fixation onsets marked as before. Note that as the saccade duration changes, the waveform shifts to remain aligned with saccade onset.)

3.2.1.5.3 Saccadic Transient Analysis and Removal

The saccade ERPs across all subjects appeared to have a transient peak around saccade onset, hereafter referred to as the peri-saccadic transient. Recent studies suggest that iEEG recordings may be contaminated with an oculomotor artifact resulting from the contraction of extraocular muscles which facilitate eye movements[247], [248]. To remove this artifact from further analysis, we employed a slightly modified procedure for removal of this eye movement artifact as described by Kovach (Kovach et al. 2011). More specifically, we used independent component analysis on all the mesial temporal lobe electrodes implanted in each patient (between 8 and 12 electrodes per patient) using the Bell-Sejnowski ICA algorithm[249] implemented in the EEGLab toolbox for Matlab[250]. The resulting components were used one at a time to reconstruct the original data, and the variance-accounted-for (VAF) between the reconstructed signal and the original signal was calculated for each of these reconstructions as shown in Equation 1 –

$$VAF = \frac{\text{var}(X_{original} - X_{reconstructed})}{\text{var}(X_{original})} \quad \text{Equation 1}$$

Here, $X_{original}$ is the original signal with the peri-saccadic spike, and $X_{reconstructed}$ is the signal reconstructed with each component, and var defines the variance of the signal. This VAF measure was only calculated for a 40ms window around each saccade event, to isolate the importance of each component towards generating the peri-saccadic transient. The VAF measure

was then averaged for all saccades, and across all MTL electrodes for each reconstruction, and then ranked from largest to smallest for all the components. Based on this ranking, the two components with the largest contribution to the peri-saccadic transient were tagged for removal. Removing the entire component significantly affected the entire ERP waveform for the different electrodes. Thus, in an effort to preserve as much of the signal as possible, a moving average interpolation was performed on the two selected components, on a 40ms window around each saccade (± 20 ms)[251]. The two modified components with the spikes removed were then used along with the non-modified components to reconstruct the original data, but with the peri-saccadic transient removed. This reconstructed data is referred to as the ICA-filtered data in all further analysis.

3.2.1.5.4 Phase Reset Simulations

To test the hypothesis that the peri-saccadic transient is part of the physiological hippocampal response to eye movements and not just an EOG artifact, simple simulations were performed to determine whether such a rapid transient response could be generated by physiological neural mechanisms. Prior work has suggested that the hippocampal response to eye movements (saccades or fixations) is generated by a phase reset or clustering mechanism, in which ongoing oscillators, in the theta frequency band, reset their phase following saccade or fixation onset. Hence, sinusoidal oscillators were simulated at every integer frequency from 1 to 200Hz with a randomly assigned phase. The amplitude of these oscillators was selected to match the power spectrum of the neural data recorded from a randomly selected hippocampal electrode. At time $t=0$, the phase of the oscillators in the theta frequency band was instantaneously reset to a predetermined phase, whereas the other oscillators continued to oscillate in accordance with their earlier phase. Temporal and frequency jitter were added to each oscillator to simulate the dynamics of real neural oscillators and to ensure that the phase alignment of the oscillators would quickly dissipate following the phase reset. The simulated neural signal “recorded” from each trial was the sum of the outputs of each oscillator. A thousand such trials were generated for each phase reset and an ERP was generated by summing the response across all of these trials.

3.2.1.5.5 Intertrial Phase Clustering

ITPC is a measure used to look at how the phase of oscillations cluster in the time-frequency domain. To calculate ITPC, the time-frequency representation of all saccade and image-onset epochs was first obtained using a short-time Fast-Fourier Transform (stFFT). Note that the saccade-onset epochs were derived from the ICA-filtered data. A Hanning window of 1000ms, in steps of 10ms, was used to reduce edge artifacts. Equation 2 was then used to obtain the ITPC value. Here, n is the number of epochs (saccade or image-onset) for each electrode, and θ_{rtf} is the phase angles of the r^{th} epoch at time t and frequency f . The calculated value $ITPC_{tf}$ is the ITPC value at a given time-frequency point.

$$ITPC_{tf} = \left| \frac{1}{n} \sum_{r=1}^n e^{i\theta_{rtf}} \right| \quad \text{Equation 2}$$

Since there were a significantly larger number of saccade epochs for each electrode compared to image-onset epochs, comparing the ITPC values between these events would have been difficult given the impact the number of events has on the calculated ITPC value. To reduce the effect of the number of events on the ITPC values, the values were transformed to ITPCz values, also known as Rayleigh's Z , as shown in Equation 3.

$$ITPC_z = n \times ITPC^2 \quad \text{Equation 3}$$

Average ITPCz values in five different, non-overlapping time-frequency windows (delta (1-3Hz), theta(4-8Hz), alpha(9-14Hz), beta(15-26Hz) and low-gamma(27-80Hz)) in the post and pre-event periods were calculated for further statistical analysis. The time duration of each of these windows in the post-event period was selected such that at least one full oscillation of the mean frequency component of each window were captured (see Table 3.2 for the precise temporal definition of these windows). Pre-event windows were chosen to be the same time duration as the post-event windows and were chosen to end 0.2 seconds before the event onset, to avoid picking up any post-event activity present before the event onset due to temporal smearing that may occur due to the selected Hanning window.

<i>Frequency Band</i>	<i>Pre-Event Window</i>	<i>Post-Event Window</i>
<i>Delta (1-3Hz)</i>	-800ms to -200ms	0ms to 600ms
<i>Theta (4-8Hz)</i>	-600ms to -200ms	0ms to 400ms
<i>Alpha (9-14Hz)</i>	-500ms to -200ms	0ms to 300ms
<i>Beta (15-26Hz)</i>	-500ms to -200ms	0ms to 300ms
<i>Gamma (27-80Hz)</i>	-400ms to -200ms	0ms to 200ms

Table 3.2| Time-frequency window definitions – This table shows the time-frequency windows that were used for analyzing the changes in ITPC and power following image-onset and saccade-onset in this paper. Note that for each frequency band, the pre and post-event windows are of the same duration. However, the window lengths for different frequency band is designed to include at least 1 cycle at the mean frequency of the frequency band of interest. Hence, the lower frequency bands (1-2Hz), will have larger window sizes than the higher frequency bands. Also, note that the pre-event windows were chosen to end 200ms before the onset of the event in an effort to avoid including any temporal smearing effects that may be present due to the short-time Fast Fourier Transform (stFFT) technique that was used to obtain the analytical signal.

3.2.1.5.6 Pre- and Post-Stimulus Power –

Spectral power was calculated for each individual epoch (saccade and image-onset) using the previously obtained time-frequency representation and then averaged across all trials for each electrode (note that the saccade-onset epochs were derived from the ICA-filtered data).

Similarly, spectral power was also calculated for each electrode-specific ERP. To investigate power changes in each trial and in each ERP, pre-event and post-event power was obtained for the five different frequency bands defined in Table 3.2, by averaging out the power in the pre-event and post-event windows. Log power change (reported in decibels) between the post and pre-event windows was calculated using Equation 4. Here, pre-event power refers to the average power in the pre-event time-frequency window and post-event power refers to the average power in the post-event time-frequency window –

$$\text{Log Power Change (dB)} = 10 \times \log_{10} \left(\frac{\text{post event Power}}{\text{pre event Power}} \right) \quad \text{Equation 4}$$

3.2.2 Quantification and Statistical Analysis

3.2.2.1 Rejected Data

Experimental data was originally collected from 11 subjects, which contributed data from 19 hippocampi and 18 parahippocampi (Table 3.1). Note that data collected from hippocampi/parahippocampi that were later found to be in the seizure onset zone was not analyzed in this study and is not included in the counts provided in Table 3.1. Data from two of the subjects had to be rejected however due to poor eye-tracker calibration, incomplete experimental blocks and insufficient data. Hence, the data reported here is from 15 hippocampal electrodes from seven different subjects and 16 parahippocampal electrodes from nine different subjects. Note that for all population-level statistical analysis performed in this study, data points were marked as outliers using the Tukey method[252] which is described as follows –

$$\text{Low outliers} = Q_1 - 1.5(Q_3 - Q_1) = Q_1 - 1.5(IQR)$$

$$\text{High outliers} = Q_3 + 1.5(Q_3 - Q_1) = Q_3 + 1.5(IQR)$$

Equation 5

3.2.2.2 Event-Related Potentials

To determine the significance of each ERP, a representative distribution of ERP maxima and minima was obtained for each electrode/ERP using non-parametric permutation testing with randomized polarity inversions (3000 permutations). ERP values were deemed significant if they fell above the 97.5th percentile of the distribution of maxima, or below 2.5th percentile of the distribution of minima.

3.2.2.3 Intertrial Phase Clustering

3.2.2.3.1 Within-Electrode Analysis

Initial, within-electrode significance of each ITPCz value was obtained using Equation 6, where n was the number of epochs used to obtain the ITPC values. This initial significance was then corrected for multiple comparisons using the Benjamini Hochberg FDR correction at the $\alpha < 0.001$ significance level. Significant portions were then masked for visualization (Figure 3.4A)

$$p_{initial} = e^{-n \times ITPC^2} = e^{-ITPCz}$$

Equation 6

3.2.2.3.2 Between-Electrode Analysis

Between-electrode statistical analysis was performed to quantify the change in phase clustering in the post-event period compared to the pre-event period. To do this, specific time-frequency windows in the pre-onset and post-onset period for each event were defined, as shown in Table 2, and described earlier. The average ITPCz values from these windows were compared between all electrodes using a Paired, two-tailed T-test, corrected for multiple comparisons using the Benjamini Hochberg FDR correction at the $\alpha < 0.01$ level.

3.2.2.4 Spectral Power Analysis

The average power in the pre-and post-event period was obtained for five different frequency bands described earlier and shown in Table 2. The log power change was then calculated for each frequency band using equation 4. A two-tailed, one sample T-test was used to test the null hypothesis of zero power change following event onset. The significance values obtained using

these tests were corrected for multiple comparisons using the Benjamini Hochberg FDR correction at the $\alpha < 0.01$ significance level.

3.3 Results

3.3.1 Visual Search Behaviour

We used a previously reported behavioural paradigm (a change-blindness task) with a new set of participants that incorporates image onset and saccadic search, and has been shown to be MTL dependent[243] with neuronal correlates to search and memory localized to the hippocampus[218], [253], [254] (Figure 3.1). In this task, scenes were presented with the goal of finding the changing object in the scene. At the start of each trial, each participant fixated on a fixation cross in the middle of the screen, after which a scene, with a hidden target, was presented, subsequently referred to here as image-onset (see Star Methods for more details). All participants actively searched the scenes for the hidden target. Each participant contributed between 3000 and 21000 saccades/fixations across all experimental trials (see Table 1). Saccades had a median duration of 9ms, and fixations had a median duration of 242ms (Figure 3.2B). Local field potentials were recorded from 15 hippocampal electrodes from seven different subjects and 16 parahippocampal electrodes from nine different subjects (see Methods and Table 1 for more details).

3.3.2 Fixation vs Saccade Responses

Since previous literature makes little distinction between eye-movement related responses in the MTL aligned to saccade-onset or to fixation-onset, these responses were analysed here for both alignments. Saccade-aligned and fixation-aligned responses in the MTL were nearly identical (Figure 3.2A). Saccade durations were very short (Figure 3.2B), suggesting that the saccade-onset ERPs and the fixation-onset ERPs were the same ERP aligned to two different, yet temporally proximal events. Although such short saccades are sometimes excluded from analysis or are considered to be microsaccades, they were included in the present analysis as they constituted a majority of the recorded saccades, and to ensure that the results reported here were generalizable across all saccades[255]. To determine whether the observed response

was better aligned to saccades or fixations, the saccade and fixation-onset ERPs were plotted as a function of saccade durations (Figure 3.2C and D, respectively). When saccade-onset ERPs (aligned to saccade onset) were plotted against changing saccade durations (Figure 3.2C), it was evident that the resulting ERPs remained aligned to saccade onset for varying saccade durations (i.e. vertical alignment of the contour plot in Figure 3.2C), suggesting that the response was aligned to saccade onset. To confirm this, the fixation-onset ERPs were plotted against preceding saccade durations (i.e. duration of the saccade preceding each fixation) in a plot aligned to fixation onset (Figure 3.2D). In this plot the observed fixation ERPs were still aligned to the saccade onset and not to the fixation onset (i.e. diagonal alignment of the contour plot in Figure 3.2D), further suggesting that the observed response was indeed a saccade-aligned response. Since the neural response to eye movements was determined to be aligned to saccade-onset, only the saccade-onset and image onset ERPs were further analyzed.

3.3.3 Analysis and Removal of the Peri-Saccadic Transient

Saccade-onset ERPs across all analyzed electrodes contained a rapid transient response with a peak just prior to the onset of the saccade response (Figure 3.2A and Figure 3.3A/B left panel) which is known to arise from extra-ocular muscle contraction[247], [248], [256]. This is clearly evident in Figure 3.2C as the sharp brief voltage transient aligned to onset of saccade. Therefore, it was important to confirm that this transient was a volume conducted potential that is not part of the MTL response. To determine if this peak arose from volume conduction of muscle activity from the extraocular muscles, the spatial distribution of the peak-to-peak voltage of this transient was plotted across all the intracranial electrodes (see Appendix A Figure S1 for a representative patient). These spatial distributions revealed that the transient was largest in the electrodes closest to the anterior temporal poles, which are also the ones closest to the orbit, providing strong evidence for this transient reflecting the potential associated with ballistic eye movements (electrooculogram - EOG). Plotting the root mean squared (RMS) amplitude of this peri-saccadic transient as a function of distance from the eyes showed that the amplitude of the transient decayed exponentially with increasing distance from the eyes, further suggesting that it is indeed a volume conduction artifact arising from oculomotor activity (See Appendix A Figure S2 for details). Furthermore, previous work has shown that hippocampal recordings can contain eye movements artifacts, with waveforms and durations very similar to the transient observed in

the current study[247], [256]. To test the alternate hypothesis that the transient was part of the physiological hippocampal response to eye movements, simulations were performed to determine whether a theta frequency phase reset mechanism (which has been previously reported as a potential mechanism through which the hippocampus responds to eye movements[198], [199]) can generate a high-frequency transient similar to the one that is seen in this study. The simulations demonstrated that a theta frequency reset mechanism can indeed generate a high-frequency transient depending on what phase the oscillators reset to (Figure 3.4A). However, the transient generated through this mechanism did not have the biphasic waveform seen in the saccade related ERPs, arguing that the peri-saccadic transient seen in the current intracranial data is not generated through theta phase resetting. Interestingly, the simulated data showed broadband phase clustering around stimulus onset, despite being generated using a pure theta phase reset mechanism (Figure 3.4B). This was likely due to the high-frequency transient that was present in the simulated signals[257], [258]. This suggested that the high-frequency transient present in the recorded MTL response to eye movements would also skew the phase clustering metrics used for comparing the saccade-onset and the image-onset responses, further warranting its removal. Therefore, a modified version of the artifact-removal algorithm developed by Kovach and colleagues was used to remove the transient from all further analysis (see methods for details)[247], [251]. The removal of this transient substantially reduced peri-saccadic power in the 20-200Hz frequency band (in a 40ms window centred around saccade onset), which has been previously reported to be the frequency band in which a majority of the power of the intracranial EOG artifact resides[247]. The middle panels of Figure 3.3A and B show representative and grand average ERPs from hippocampal electrodes after this peri-saccadic transient was removed. Note that for all succeeding analysis of the saccade-onset response, the ICA-filtered data was used. Blink-related ERPs were not contaminated by the same high frequency transient that contaminated the saccade-related ERPs (Figure S3), providing further evidence that the peri-saccadic transient described above is likely generated by the intraocular muscles involved in eye movements.

3.3.4 Event-Related Potentials (ERPs)

To compare the temporal dynamics of the MTL response to saccade-onset and image-onset, event-related potentials (ERPs) were generated for both events. For each selected

electrode, we calculated the average of the event-aligned response across all the trials, and across all experimental blocks. Non-parametric permutation testing was used to test the significance of this response. Figure 3.3A shows the ERPs for a representative hippocampal electrode for saccade epochs (left), ICA-filtered saccade epochs (middle) and for image onset epochs (right). 13 out of the 15 (86%) analyzed hippocampal electrodes had a statistically significant peak or trough following saccade onset and all hippocampal electrodes (100%) had a statistically significant peak or trough following image onset. Similarly, all parahippocampal (PHG) electrodes (100%) had a significant peak or trough following saccade onset and image-onset (Appendix A Figure S7). The MTL response (hippocampal/PHG) to saccade-onset was more rapid compared to the image-onset response, which is evident from Figure 3.3. It is important to note that the observed ERPs had different amplitudes across subjects which is evident in other work[194] but may also have been influenced by the fact that the current analysis included all stimuli, without separating old and new items, and hits and misses, all of which have been shown to influence the amplitude of the image-onset response[190], [191], [194], [197], [218], [219]. Blink event related potentials were analyzed for all subjects. Blink ERPs were characterized by a large trough ~100ms following blink onset and had a markedly distinct waveform when compared to the saccade or image-onset ERPs (Figure S3), suggesting that blink ERPs neither contaminate the saccade-onset nor the image-onset ERPs. To further characterize the difference in the image-onset and saccade-onset responses, the phase clustering following stimulus onset was investigated.

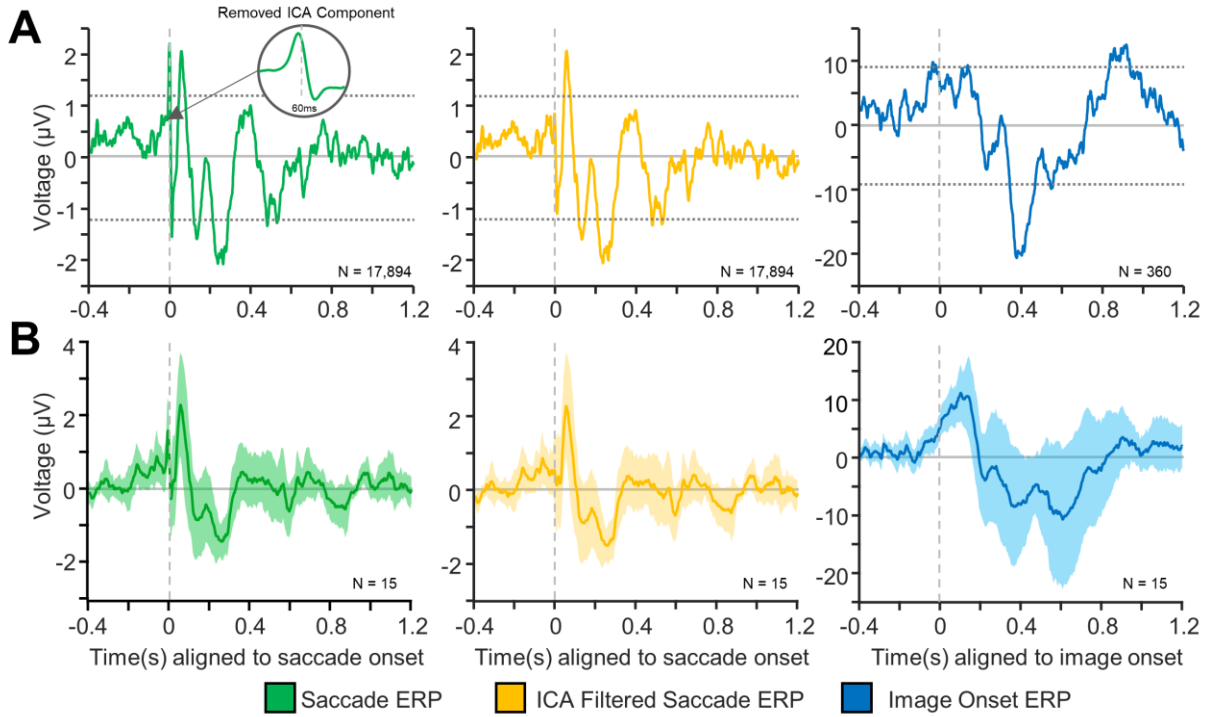


Figure 3.3 | Event-related potentials (ERPs) following saccade and image onset: A) Representative ERPs from a hippocampal electrode for saccade aligned epochs (left), saccade aligned ICA-filtered epochs (middle) and image-onset aligned epochs (right) from the same electrode. The dashed horizontal lines mark significance bounds generated using permutation testing (3000 permutations) with randomized polarity inversions (see Methods). The inset in the left-most figure (green) shows the average of the ICA-components (in a 60ms window surrounding saccade onset) that were removed in order to obtain the ICA-filtered saccade onset ERP. Note that the ICA-Filtered ERPs (middle pane) are obtained by removing the peri-saccadic transient from the saccade ERPs (left pane) (see Methods for details) B) Grand average ERPs for original saccade epochs (left), ICA-filtered saccade epochs (middle) and image-onset (right) epochs. The filled in region indicates 95% confidence intervals for each plot. Note that the ICA filtering successfully removes the transient, peri-saccadic response seen in the saccade aligned ERPs (middle panel) while maintaining the integrity of the remaining ERP.

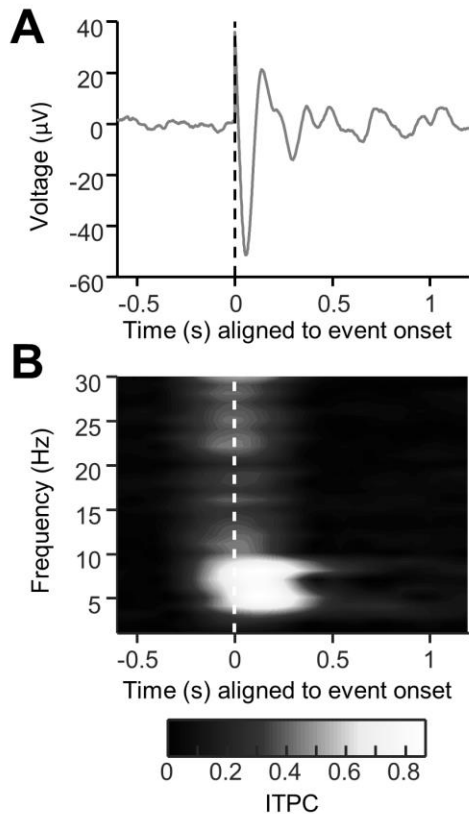


Figure 3.4 | Theta phase reset simulation: A) An ERP generated by simulating a theta-band phase reset mechanism (see Star Methods). Phase was reset to a pre-selected phase (in this case, to $\frac{4}{5}\pi$ or 144°). Notice the sharp, high frequency transient that is present in the ERP at time $t=0$ despite being generated using a low-frequency phase reset mechanism. **B)** The intertrial phase clustering of the same simulated data as in A. Notice that despite the mechanism of the response being a low frequency reset, broadband phase concentration is seen, suggesting that high frequency transients in the data can skew intertrial phase clustering metrics to show artificial, high frequency phase clustering that isn't present in the underlying data.

3.3.5 Phase Clustering

If, in the presence of an ongoing oscillation, phase clustering occurs following stimulus onset, then phase-resetting is considered the mechanism giving rise to the ERP. Hence, ITPC was measured for saccade-aligned epochs and for image-onset aligned epochs. This measure assesses the distribution of the phase at each time point across trials and gives a value between 0

(no phase clustering, uniform phase distribution) and 1 (complete phase clustering). In this case, the ITPC value has been converted to an ITPCz value to control for the different number of trials for different electrodes/stimuli. The higher the value of the ITPCz, the higher the phase clustering. As evident from Figure 3.5, there is a stark contrast in the phase clustering following saccade and image-onset events. Significant hippocampal phase clustering was observed in the delta (1-3Hz), theta (4-8Hz) and alpha (9-14Hz) frequency bands. Significant hippocampal phase clustering was also observed following image-onset, however, it was largest in the delta frequency band and small, albeit significant, phase clustering was also observed in the theta and alpha frequency bands. The same analysis performed on all the parahippocampal electrodes (see Appendix A Figure S5) revealed qualitatively similar results. It should be noted that the ITPC analysis reported here was performed on the ICA-filtered saccade-onset aligned epochs. When a similar analysis was performed on the original saccade-onset aligned epochs, broadband phase clustering was observed, likely due to the high-frequency peri-saccadic transient that was present in the original data. Although these results suggest significant phase clustering following image onset and saccade onset in the mesial temporal lobe structures, phase clustering can also be induced by an additive/evoked response that is added to ongoing oscillations at the onset of the stimuli[259]. To differentiate between this additive response and a true phase-reset response, the pre- and post-stimulus power was measured for individual trials and for the ERP.

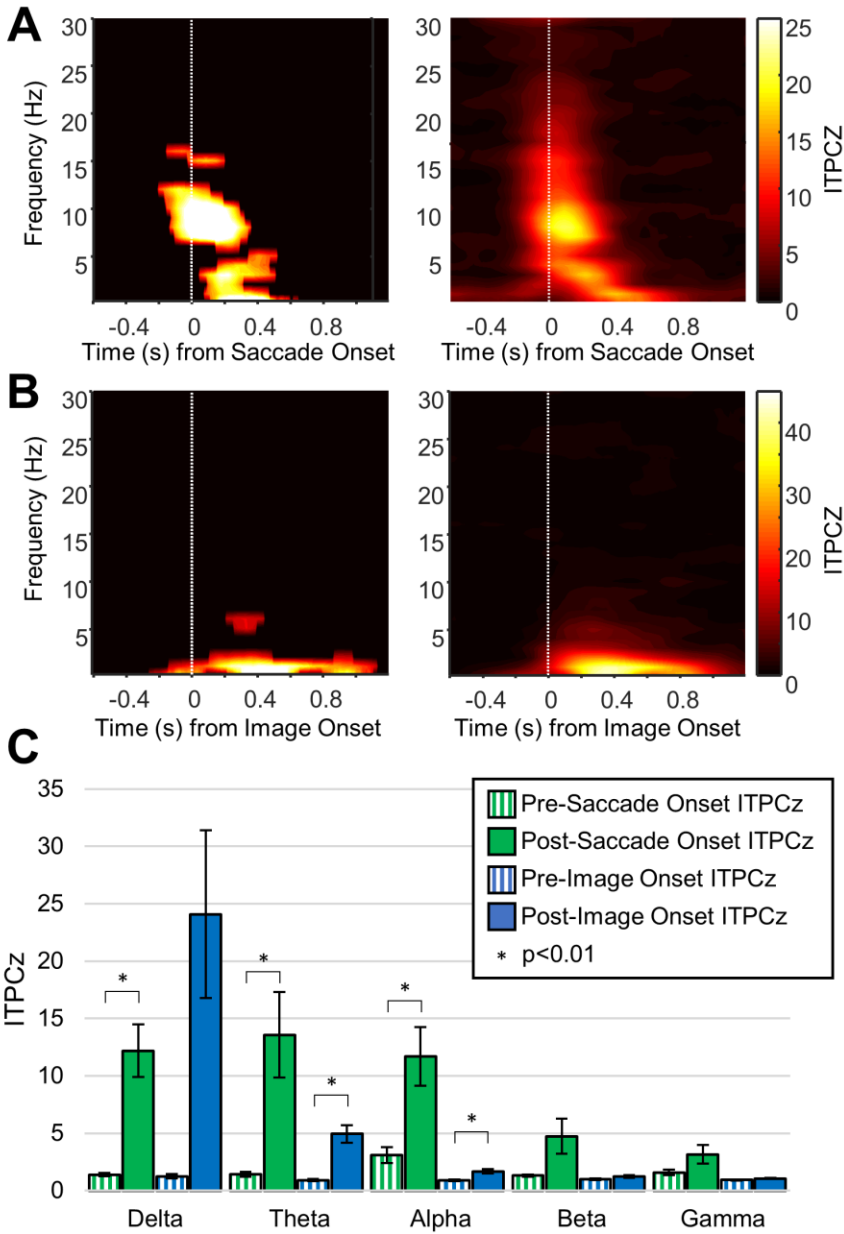


Figure 3.5 | Intertrial phase clustering (ITPC) for hippocampal electrodes: A) Left - Representative ITPCz for ICA-filtered saccade-aligned epochs. The plot has been masked to indicate significant values (see Methods for details). Right – Grand average ITPCz value for ICA-filtered saccade aligned epochs for all hippocampal electrodes. Note the obvious phase clustering in the delta, theta and alpha frequency bands. B) Same as A but for image onset aligned epochs. Notice that the phase clustering is limited to lower frequency bands and has a longer time course. C) Comparison of ITPCz values for different time-frequency windows in the pre and post event periods (see Table 2). Significant differences are marked with an asterix.

3.3.6 Power Changes

To investigate whether the observed phase clustering following saccade and image-onset events was due to a phase reset, the pre- vs post-event power was compared in the individual trials and in the ERP. For a pure phase-reset dependent ERP, there should be no power changes within each trial but there should be a significant increase in power following the event in the ERP. This is precisely what was observed for saccade responses (Figure 3.6A). There was no difference in spectral power in the individual trials across any of the frequency bands (Figure 3.6A-left and 3.6C), but there was a significant broadband increase in power (in the delta, theta, alpha, beta and low-gamma bands) following saccade onset in the saccade ERP (Figure 3.6A-right and 3.6D). Conversely, all the significant power changes in the image-onset ERP were mirrored by significant power changes in the individual trials (Figure 3.6B, C and D). This suggests that the image-onset response is not a characteristic phase reset, as there appears to be an addition of power to each individual trial following image onset, in contrast to the saccade response, which better fits the characteristics of phase resetting across the delta, theta and alpha frequency bands.

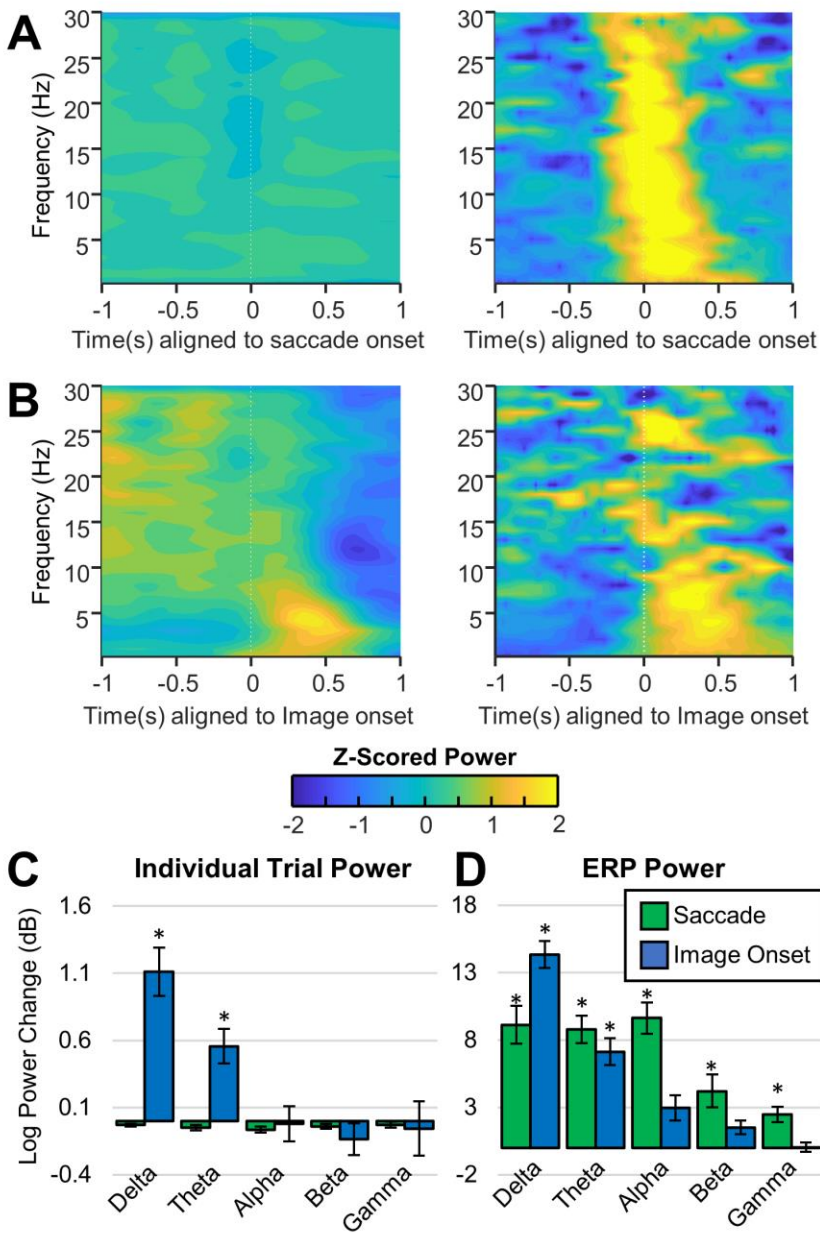


Figure 3.6 | Spectral power for saccade-onset and image-onset epochs for hippocampal electrodes: A) & B) show power spectrograms in which the power for each frequency has been z-scored to better visualize power changes within each frequency. **A: Left:** Average Power of ICA-filtered individual saccade aligned epochs across all hippocampal electrodes. **Right:** Average power of ICA-filtered saccade-aligned ERPs averaged across all hippocampal electrodes. Notice that despite the significant increase in broadband power observed in the saccade ERPs, there is no observable increase in power in the individual trials. **B: Left:** Average power of individual image-onset aligned epochs across all hippocampal electrodes. **Right:** Power of image-onset aligned ERPs averaged across all hippocampal electrodes. Note that there is an observable increase in delta-band and theta-band power in the ERP and in the individual trials following image onset. **C)**

Average log power change ($10\log_{10}(\text{post event power} / \text{pre event power})$) between pre and post event time-frequency windows (see Method Details for definition of the time frequency windows). Significant differences are indicated with an asterix. Notice that there is no significant change in the power following saccade onset, but there is a significant increase in the power of the individual trials in the delta and theta bands following image onset. D) same as C but for the power of the ERP. Note that in the ERPs, there is a significant increase in broadband power following saccade onset and a significant increase in lower frequency power (delta and theta) following image onset.

3.4 Discussion

In this study, iEEG recorded responses to image presentation and eye movements were investigated in the human MTL. These responses were characterized by investigating the underlying spectral characteristics of the corresponding event related potentials (ERPs). It was demonstrated that the MTL response following image presentation is a slow, evoked potential with corresponding phase clustering and power increases primarily in the delta band (Figure 3.5 and 3.6). In contrast, the MTL response following eye movements was a faster response with phase clustering but no within-trial power increases. This eye movement-response was observed to be aligned to the onset of the saccade and not to the termination of the saccade (fixation) (Figure 3.2). These findings suggest that there are distinct mechanisms through which saccade and image onset these responses are generated, and the implications of these findings in the context of visual memory are discussed below.

3.4.1 Evoked Image-Onset Response

The image-onset ERP observed in this study was a slower potential than the saccade related ERP with a first trough occurring at 400-600ms, similar to the AMTL-N400 response that has been observed in the MTL and the PHG following the presentation of word stimuli[191], [197], [219], [260] and had similar temporal characteristics as previously reported MTL response to visual stimuli [194] (Figure 3.3). Similarly, ERPs associated with probe presentation during a Sternberg task, demonstrated a late negative component, similar to this study but without the associated positive p300 component[228].

The image-onset response observed in this study was accompanied by significant phase clustering in the theta and alpha bands. Additionally, the post-image onset phase-clustering was accompanied by an increase in theta and delta power (in individual trials and in the ERPs) with a latency of approximately 250-650ms. Together these observations suggest that the image-onset response is in large part an evoked response[219], and represents recruitment of additional neuronal populations[260]. This interpretation is consistent with observations that ERP amplitude, but not phase clustering, is decreased in hippocampal sclerosis (HS)[260]. Since the hallmark of HS is CA1 cell loss[261], the reduction of the ERP amplitude in HS is likely directly related to the number of CA1 neurons that can be driven to threshold, as well as the number of synaptic contacts that can be made on them. The number of synaptic contacts will directly change the magnitude of the local field potential, as it is largely a manifestation of post-synaptic potentials (PSPs), which decrease in HS due to a reduction in the number of available synapses. Furthermore, since phase-clustering was not reduced[197], [260], a decrease in neuronal synchrony is unlikely to explain the decrease in ERP amplitude[262] in HS. At the cellular level it would be expected that an evoked response should be accompanied by an overall increase in cellular firing rates. Indeed studies have shown a marked firing rate increase at image onset peaking ~300ms after stimulus onset[221], [263], which is consistent with the latency of the image-onset ERP seen here(Figure 3.3). Our interpretations regarding the image onset ERP are consistent with a recent study that demonstrated an image-onset response very similar to the response observed here and characterized it as an additive/evoked response based on the amplitude/power and phase changes discussed earlier[259]. In summary, the image onset response that we observe appears to be a slower potential, with different frequency components than the saccade related ERP, and likely represents an evoked response[259] that involves excitability increases of additional neurons.

3.4.2 Phase-reset following Saccade Onset

Eye-movement related responses have been previously analyzed following saccade-onset[195], [198] and fixation[199], [264], [265]. Here we were motivated by the work of Ito and colleagues who have shown that self-initiated saccades during the viewing of natural scenes were associated with phase resetting of the LFP within the beta frequency band, or in the theta band with a blank screen in area V1 of the macaque[266]. Concomitant single unit recordings

disclosed that the resetting was not associated with an increase in spike firing, but in fact was explained by a change in spike timing. They concluded that that the early (~75ms) LFP changes in V1 were likely the manifestation of eye movements associated corollary discharges (CD), whereas single unit firing rate changes were a manifestation of visual input. Similar findings have been demonstrated in area TE/STS[224], [227], and area V1[264] in complete darkness, which suggest that the saccade related ERP is likely an modulatory input that phase resets ongoing oscillations.

In this context we have demonstrated that in the human MTL, the saccade associated ERP represents a phase-locking to saccades onset and not its termination (i.e. fixation) (Figure 3.2). Like others, we interpret these findings to imply that the post-saccade ERP arises not as a result of visual reafference, but a modulatory input like a corollary discharge that is transmitted from gaze control centers to mnemonic structures in addition to a number of other areas of the brain like FEF, TE, V1, and entorhinal cortex (EC) [225]–[227], [266], [267]. Although it may be argued that our LFP analysis is too insensitive to definitively argue the ERP is comprised of a corollary discharge, prior work has shown that the saccade-associated LFP is reflective of eye-movements, whereas post-saccade firing rate changes reflect visual input[266] .

Support for the speculation that a corollary discharge may be present in mnemonic structures comes from single unit studies in non-human primates (NHP), which have revealed the presence of saccade direction (SD) cells, some of which increase their firing rate as early as 68ms prior to the saccade[268]. Previously, the same group reported saccade-related phase resetting of theta oscillations within non-human primate hippocampus during free-viewing, although no LFP data was presented in their more recent paper on SD cells[268]. It would be interesting to understand if theta phase resetting occurs in the entorhinal cortex of the non-human primate, and the relationship of the SD cells to such ongoing population activity. Nonetheless, their hippocampal phase resetting effect was not associated with increases in spiking rate ([198] Fig 1D), consistent with a modulating effect (as opposed to driving)[241] of a corollary discharge, as has been previously suggested in area TE of the NHP[227]. Such large-scale, cross-modal control via modulating inputs (phase resetting) has been suggested to be mediated through thalamic relay nuclei[242], which is further supported through anatomical connectivity between

the memory and oculomotor networks[165]. For entorhinal cortex SD cells, such a pathway via LD nucleus of the thalamus has been suggested as the route by which saccade direction information, possibly similar in content to the information transmitted to lateral inter-parietal sulcus[269], reaches the entorhinal cortex[268]. Since the entorhinal cortex represents a major input to the hippocampus[270] hippocampal phase resetting associated with saccadic eye movements may arise from the transmission of SD cell information to area CA1 of the hippocampus.

That the saccade related phase-resetting starts with the onset of the saccade is strong evidence that corollary discharge[227], [266] underlies its generation, and argues against visual reafference. Furthermore, our finding that blinks manifest as a starkly different electrophysiological response in the human MTL when compared to the saccade-aligned response (Appendix A Figure S3) suggests that blink ERPs do not contribute to the saccade-related response in the human MTL. These results further suggesting the saccade-onset ERP is an unadulterated manifestation of a saccade onset related signal, very much like a corollary-discharge. However, additional characteristics of the response would be required to confirm its identity as a corollary discharge. Specifically, corollary discharges associated with saccadic eye-movements tend to be directional, and thus have different waveforms depending on the direction of the saccade (whether it is ipsiversive, or contraversive to the recording site). Furthermore, a saccade-related corollary discharge should be present in the dark. Although we have not shown this in our patients since obtaining complete darkness in the clinical setting is problematic, a number of studies have shown that both the LFP[271], and single unit activity in the NHP hippocampus[272] are modulated by saccades in complete darkness.

Although a number of studies in humans and NHPs have demonstrated both saccade related ERPs[198], [199], and alterations in single unit activity with saccadic eye movements[224], including those recording from the hippocampus, our analyses have allowed us to critically add to this literature by suggesting that the hippocampal ERP is associated with saccade onset, implying that it may arise from a corollary discharge[227], [264], [266]. What might be the role of such a corollary discharge within the hippocampus? Analogous to the discussion regarding SD cells in the entorhinal cortex[268], such saccade direction information

may be useful for creating ‘mnemonic maps’ from visual stimuli, a process that requires knowledge of the viewing order, and spatial placement of the visual information. Additionally, corollary discharges in some regions of the brain provide the remapping transformation from the current receptive field (RF) of a neuron to the future field (FF) of the neuron[269]. Envisaging the hippocampus as a comparator[76], [273] of internal representation (via CA3 inputs) to current information (EC → CA1), and in the context of predictive-coding[274], the remapping of current receptive fields to future fields in LIP[269], may by analogy represent the comparison of the future mnemonic representation (prediction) of the visual stimulus to the mnemonic representation of the current visual stimulus within the hippocampus. This remains speculative, and future work will be required to understand the mechanistic role and information provided by such a phase-resetting/corollary discharge mechanism in the hippocampus beyond the temporal changes in excitability that accompany phase-resetting[121], [183], [189], [275]

Lastly it is important to note that saccade related phase-resetting was observed in other MTL sites such as the PHG which is known to play a role in visual search behavior (Appendix A Supplementary Figures 4-6). For instance, parahippocampal damage has been previously shown to alter visual search behavior, leading to increased number of saccades and visual neglect[173], [276]. This is consistent with the previously cited literature that suggests anatomically widespread phase resetting associated with saccadic eye movements[195], [198], [199], [227], [266]. This is not surprising if such saccade associated phase resetting is needed for preparing disparate brain regions for processing of new salient visual stimulus for information coding[185], storage[121], [189], [275], and sensory integration[183].

3.4.3 Comparison of the two responses

The saccade-related ERP stands in stark contrast to the image-onset ERP that we observed, with the image onset response manifesting as an additive/evoked response, while the saccade response is better described as a phase resetting. At the cellular level it would be expected that an evoked response should likely demonstrate greater firing rate increases following image onset, which should occur later in time given its low frequency, whereas the saccade related ERP would likely not be accompanied by an increase in firing rate, would occur sooner after a saccade than the evoked response, and should show spiking phase-locked to the

reset oscillation. Although there are limited studies to address this, a human single unit study by Andrillon et al (2016) comparing single unit image onset responses to saccade related responses demonstrated a 100% increase in firing rate after image onset, peaking at 300ms, while saccade related responses demonstrated an earlier increase in spiking, and a more modest firing rate increase of 25-30% following a saccade[221]. Additionally, in the NHP hippocampus, an increase in firing rate is seen following image onset in the same task as the one used here, along with an evoked response and low-frequency phase clustering[218], [221], [253], similar to the response reported in the current study. Although the human single unit data do suggests a modest increase in firing rate following a saccade, an excess of spike synchrony induced by a modulating input may underlie an increase in apparent firing rate[266] following saccades in humans[221] by biasing spike timing[277], [278], and not increasing firing rate per se. Lastly and likely most importantly, the local field potential (LFP) is largely a manifestation of post-synaptic potentials, the extent of their synchronization[279], and any associated spiking activity[280]. Recently it has been shown that the LFP is an excellent surrogate for predicting the contributions of post-synaptic currents to membrane potential fluctuations[281] , and specific to our context, Ito and colleagues suggest that the early component of LFP following a saccade is an eye movement related potential and does not arise from visual reafference. Furthermore, cortical excitation has been observed following a saccadic eye movement in V1 in darkness, which likely arises from a post-inhibitory rebound[264], [272]. Hence, we suggest that: 1) the LFP we observe following a saccadic eye movement has an extra-hippocampal origin that modulates the timing of hippocampal spiking but does not directly drive neurons to threshold; 2) it, like the responses in V1, are driven by an initial post-synaptic inhibition followed by rebound excitation[264], [272]; 3) the rebound spiking acts non-locally (i.e.. projects to other brain regions) and thus itself does not contribute to the LFP recorded within the hippocampus and thus a power increase is not observed early after a saccadic eye movement and; 4) the image onset response reflects driving inputs from extra-hippocampal sites, likely entorhinal cortex, that are known to excite hippocampal neurons through glutamatergic synapses[270], [282]–[284]. Future work will be required to elucidate the validity of these propositions.

3.4.4 Saccade related phase resetting is not an EOG artifact

Emerging evidence points to the presence of EOG contamination in iEEG recordings. We have thus endeavored to address this in a number of ways, which led us to conclude that the characteristics of the saccade related ERPs arise locally within the MTL and are not volume conducted eye movement artifacts. The various lines of evidence are: 1) The duration of the EOG artifact, which is ~ 20ms around saccade onset, can not contribute to the phase resetting that we observe, since the latencies for the phase resetting are an order of magnitude longer; 2) As evident from a number recent publications[247], [248], [256], EOG artifacts contribute to power increase in the 20-200Hz frequency band, not within the theta frequency band we demonstrate our effects in. Since our primary findings are not concerned with these frequency bands, the presence of the artifact is not directly relevant to our findings; 3) We have undertaken a number of additional steps to remove the artifact using the detailed methodology identified by [247]). The only difference between our artifact removal approach and the one identified by Kovach et al. is that we did not employ bipolar referencing. This decision was not haphazard, since the majority of saccade related electrophysiology literature employs unipolar referencing, and present our findings consistent with this literature; and, 4) We demonstrate by analyzing the RMS amplitude of the artifact and that of the resetting response as a function of distance from the eyes (Appendix A Figure S2), the RMS amplitude of the artifact decays exponentially with distance from the eyes (i.e. proportional to r^{-2}), whereas the RMS amplitude of the response does not. This clear dissociation between the effect we are reporting and the EOG artifact provides unequivocal evidence that the phase resetting response is not artifactual.

3.5 Conclusion

In this paper, the field potentials following saccade onset, fixation onset and image-onset were characterized using the temporal nature of the average MTL response, event-related phase clustering, and spectral power changes. Image-onset responses were shown to have low-frequency phase clustering and within-trial power increases, suggesting an additive/evoked neural response. In contrast, the saccade-related response was aligned to saccade onset, with significant phase clustering across the delta, theta, and alpha bands, and no within-trial power

changes consistent with a phase-reset mechanism for the saccadic response. We propose that the saccade-onset response and image onset response are dichotomous, with the saccade-related response likely representing a corollary discharge that modulates hippocampal activity, whereas the image-onset response arises from driving sensory-related signals to the MTL. Future work will require further characterization of saccade related potentials at behavioral, and electrophysiological levels (LFPs and single units), specifically their generation in the dark, their directional dependencies, and the neuronal current sources in these regions. Our work has implications for memory-related testing and neuromodulation, since visual search is likely to engage different hippocampal mechanisms than would visual stimuli presented only during fixation.

3.6 Author Contributions

Conceptualization, C.K., and T.A.V.; Methodology, O.T. and K.H.; Software, C.K., O.T. and K.P.; Formal Analysis, K.P. and C.K.; Investigation, O.T., C.K. and K.P.; Data Curation, O.T., C.K. and K.P.; Visualization, K.P.; Writing – Original Draft, C.K. and K.P.; Writing – Reviewing and Editing, C.K., K.P., and T.A.V.; Funding Acquisition, K.H. and T.A.V.; Resources, T.A.V.; Supervision, K.H. and T.A.V.

4 Corollary Discharge: Eye Movement is an internally generated timing signal

The material in this chapter has been adapted from a preprint[285] and publication in progress and is reproduced with permission.

Chaim N. Katz*, Andrea G.P. Schjetnan*, Kramay Patel*, Victoria Barkley, , Kari Hoffman, Suneil K. Kalia, Katherine Duncan, Taufik A. Valiante (2021). A corollary discharge mediates saccade related inhibition of single units in mnemonic structures of the human brain

4.1 Introduction

Humans rely on vision to understand their environment[286], [287], and their primary tool for exploration is the saccade[288] – a ballistic movement of the eyes from one point of fixation to another. Given their importance, it may seem intuitive that saccades are inextricably linked to memory[152], [154], [160], [165], [166], [243], [289], [290] and are even associated with prominent electrophysiological responses[198], [199], [216] in memory related mesial temporal lobe (MTL) structures. Yet, the cellular mechanisms through which the oculomotor system influences the human MTL remain largely unknown, hindering the understanding of *how* eye movements interact with the memory system. In vision, saccade related motor signals in the form of a corollary discharge (CD) prepare the brain for the sensory consequences of a planned movement[225], [291]. Our and others' recent local field potential (LFP) recordings provide preliminary clues that saccade related responses in the human MTL may also reflect a CD-like signal. Specifically, we previously demonstrated that saccade related MTL ERPs are unlikely to reflect visual exafference; visual and saccade related activity displayed different oscillatory profiles and saccade related phase resetting was time-locked to the onset of the motor (saccade)

initiation and not the onset of new visual information (fixation)[216]. Moreover, saccadic modulation of MTL electrophysiology has been shown to persist in the dark[221], [271], [272], again suggesting that the MTL modulation likely arises from internally generated signals like a CD. However, a more direct assessment of the CD hypothesis requires recording individual neurons within the human MTL to assess core properties of a CD-like mechanism underlying the saccadic eye movement (SEM) related MTL modulations.

In the most rudimentary implementation of a CD, a copy of the initiating motor command suppresses the sensation produced by action[267], [292], [293]. In this implementation, the circuit motif consists of axon collaterals of primary motor neurons synapsing onto inhibitory interneurons, which inhibit sensory neurons during the movement[225], [291]. Increasingly complex variations on this motif have been presented for the CD-like discharges across the phylogenetic tree; however, inhibition remains a key mechanism by which CDs mediate their effects[225]. Indeed, within the taxonomy for CDs proposed by Crapse and Sommer, the saccadic inhibition/suppression of visual cortical excitability[294] comports well with the inhibition and sensory filtering function of a lower-order CD. This saccadic suppression is thought to be a requirement for registering a stable visual percept of the world by blocking visual input during ballistic eye movements (although alternative hypotheses exist for the observed saccadic suppression[295]).

Additionally, CDs are thought to help produce a stable visual percept by dynamically shifting receptive fields in anticipation of ensuing eye movements (for a full review, see [296]). These CDs thus appear to contain information about the direction and magnitude of ensuing saccades. Such a higher-order CD facilitates the transformation of the motor signal to visual coordinates, necessary for anticipatory adjustments of neuronal receptive fields and updating spatial locations[267]. Such a function is well exemplified by its disruption; inhibiting the mediodorsal nucleus, a known node in a higher-order CD circuit, degraded non-human primate's (NHP) conscious perception of a target shift[297].

In NHPs, CD's have been proposed as the source of directional information in the entorhinal cortex (EC), and to play a role in spatial mapping within EC[268], [298]. These studies suggest further research is needed to evaluate the CD hypothesis within the human brain since only

circumstantial LFP evidence exists for a CD mediating SEM-related MTL modulations in humans[198], [199], [216], [227]. Thus, despite LFP support for the presence of a CD within MTL structures, such a hypothesis remains wanting of support at the cellular level[299]. Based on the CD literature[225], [294], [297], [299], [300], we propose a framework for amassing evidence of a CD in the human MTL. First, since CDs reflect the anticipatory modulation of sensory and/or higher-order structures, a SEM-related CD in the MTL must modulate firing rates before or during the saccade. Second, since most rudimentary CD circuits involve a prominent inhibition of sensory input, CD-related modulation of MTL activity should be largely inhibitory, evidenced by a decreased firing rate of putative pyramidal neurons and/or increased firing rate of putative inhibitory neurons. Third, there is extensive evidence of the modulation of single unit activity (SUA) in the MTL to visual stimuli[263], [301]–[304]. Thus, any CD-related modulation of activity in the MTL should be distinct from modulation associated with visual input. Finally, as part of an oculomotor circuit, CDs should represent the directional parameters of the ensuing movement. Thus, the CD-related modulation of SUA within the MTL must demonstrate directional tuning (i.e., dissociable neuronal responses to ipsiversive and contraversive saccades).

Within this framework, we leverage the unique opportunity of recording SUA from epilepsy patients undergoing diagnostic stereo-electroencephalography (sEEG) to investigate whether an SEM-related CD pervades the human MTL. While the participants visually searched natural scene images, we simultaneously recorded SUA from the hippocampus and related MTL structures along with eye movements. We utilized these recordings to characterize peri-saccadic SUA according to our four criteria, both within the MTL and serendipitously-obtained recordings from the medial occipital lobes, as a control region, in two patients. Based on the above criteria and recognizing the limitations of human-related research, we provide evidence of an SEM-related CD that modulates SUA in the human hippocampus and other related MTL structures.

4.2 Methods

4.2.1 Participants

Eleven individuals with medically refractory epilepsy participated in this study (Table 4.1). As part of their clinical assessment, sEEG electrodes (Ad-Tech Medical, WI, USA) were implanted in clinically determined sites to ascertain their candidacy for surgical resection of an epileptogenic focus. If patients consented to the implantation of microwires as part of the research, then the sEEG macro-electrodes were supplemented with microwires (Ad-Tech Medical, WI, USA). The Research Ethics Board of the University Health Network approved this study.

Table 4.1| Participant summary table. Data for each participant is shown in the respective rows. HC: hippocampus; AM: Amygdala; PHG: Parahippocampal Gyrus; OCC: Occipital areas

ID	Sex	Age	Sessions	# Saccades	HPC units	AM units	PHG units	OCC units	Total units
P89	F	45	1	538	13	14	30	0	57
P90	M	20	1	414	11	22	0	98	131
P91	F	59	1	463	2	3	0	0	5
P100	F	19	1	527	25	1	0	0	26
P101	F	25	1	625	32	6	10	0	48
P103	M	49	1	558	3	0	0	0	3
P107	F	64	1	641	0	9	1	0	10
P109	M	28	1	593	36	8	0	0	44
P116	M	28	1	555	21	58	0	0	79
P125	M	24	2	628	14	43	63	21	141
				821	8	22	22	6	58
P126	M	25	1	589	45	0	2	0	47
Total					210	186	128	125	649

4.2.2 Experimental Design

The terms "neuron" and "unit" are used interchangeably. To characterize SUA in the time interval surrounding SEMs, we developed a task that involved image presentation and target search (Figure 4.1A) to engage participants in generating SEMs. The encoding session was divided into 40 trials, each consisting of a fixation cross (1 second), followed by the presentation of an image consisting of a scene. Four copies of one of two possible targets were embedded in each scene. Participants were instructed to visually search through the scene to find as many of the targets as possible. If they found all four targets, participants were instructed to continue to move their eyes through the scene to remember and associate the target with the image. Each

image was presented for four seconds, after which participants were asked how many targets they found. The trials were grouped into blocks of 5 trials, with each block having the same embedded target. Following the encoding session, participants were presented with instructions on the ensuing retrieval session. The data presented here is based solely on eye movements during the encoding session.

Patients reclined upright in their clinical beds with a laptop computer placed at a comfortable viewing distance in front of them. An infrared video-based eye-tracker (EyeLink Duo; SR Research Ltd., Osgoode, Canada) was used to monitor and record their eye movements throughout the task (see below for details on eye-tracking).

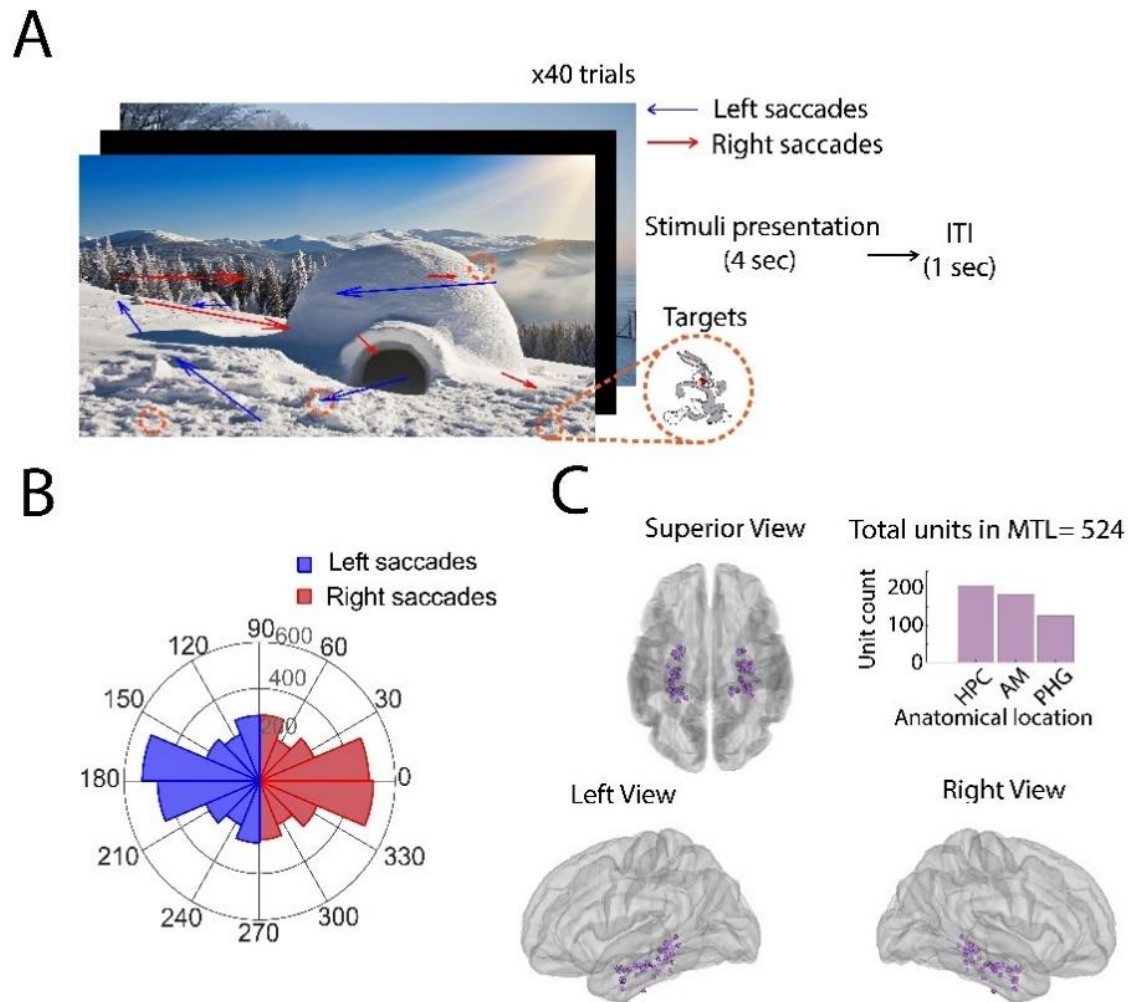


Figure 4.1| Behavioral task and recording locations: A) Visual search task: Participants searched for one of two target images (i.e., Bugs Bunny or Wile E. Coyote) in a series of pictures with natural scenes separated by inter-trial interval (ITI). Example of saccade trajectories (arrows) with saccades classified as leftward (blue) or rightward (red) during 4 seconds of image presentation. B) Leftward and rightward saccade distributions. SEM direction totals across subjects were not significantly different (paired t-test, $p=0.63$). C) Location of microwire bundles in different MTL areas. Insert: Unit counts by HC: Hippocampus, $n=210$; AM: Amygdala, $n=186$; PHG: Parahippocampal Gyrus, $n=128$).

4.2.3 Electrophysiology

Acquisition and Localization

Each commercially available Behnke-Fried Macro-Micro electrode (Ad-Tech Medical, Racine, MN) had 8 or 9 macro electrodes along the electrode shaft and a bundle of 8 embedded microwires plus one ground/reference microwire protruding from the tip[305]. Only patients with MTL electrodes and electrodes in other anatomical locations specified by the pre-implantation hypothesis were included in this study. Data were recorded with a 128-channel Neuralynx Atlas Data Acquisition System (Neuralynx Inc, Bozeman, MT). The microelectrodes were sampled at 32kHz, with a 16-bit resolution and were bandpass filtered in hardware between 0.1 and 8kHz. Each microwire signal was re-referenced locally to one of the eight wires on the same bundle as we have done previously[306]. Electrode localization was performed by co-registering pre-op MRI with post-op CT using the iELVIS toolbox[246]. Electrodes were localized and visualized in the MTL structures across patients (Figure 4.1C; For occipital localizations, see Appendix B Supplementary Figure S1A).

Spike Detection and Sorting

For offline spike detection, all microelectrode channels were bandpass filtered between 300-3000Hz. Spikes were subsequently detected using local energy measurement threshold crossings, calculated by convolving the raw signal with a kernel with the approximate width of an action potential[307]. All detected spikes were sorted using the open-source, semiautomatic template-matching algorithm OSort[305]. Similar to our previous work[306], [307], we classified clusters as putative single neurons using the following criteria (1) minimal/no violation of refractory period, (2) shape of the inter-spike interval distribution, (3) shape of the waveform, (4)

separation from other clusters; and, (5) stability of firing rate (assessed by comparing the average firing rate of the neuron to multiple null distributions obtained by randomly sampling 400ms and 5s epochs from each neuron's spike train). Groups that appeared similar to one another were merged. For extra quality control, neurons with firing rates lower than 0.07Hz were subsequently removed. Clusters that were either contaminated with noise or failed to meet the criterion described above were rejected. For the accepted clusters, the individual waveforms, along with the timestamp of each spike and its cluster definition, were saved. The insert of Figure 4.1C shows the total cells from each location detected in MTL (SUA from occipital locations is shown in Appendix B Supplementary Figure S1A)

Waveform Analysis

The shape of a waveform suggests which type of neuron produced it, with pyramidal neurons having more broad waveforms and inhibitory having more narrow[308]. We followed a similar approach to Fu and colleagues to determine the classification type of spiking activity from our single-unit recordings[309]. Each neuron's average waveform was extracted by averaging all waveforms in a specific cluster. The first trough (negative peak) and first peak times were extracted. Neurons with a trough-to-peak time of $<0.5\text{ms}$ were considered 'narrow-spiking' (NS), and $\geq 0.5\text{ms}$ were considered 'broad-spiking' (BS).

4.2.4 Analysis of eye-tracking data

The SR Research eye-tracking system was used to track participants' eye movement. The eye-tracker was placed at the bottom of the screen and connected via ethernet to a separate laptop running the behavioural task using Presentation software (NeuroBehavioral Systems, Albany, CA, USA). All participants first underwent a 13-point calibration and 9-point validation test (EyeLink Portable Duo sampled at 1000Hz, from SR Research).

Eye movements were detected using SR Research's built-in software that uses an Identification by Velocity-Threshold (IVT) algorithm. This algorithm is a velocity-based method that separates fixations and saccades based on the distance between the current and next points[244]. To be considered a saccade, the velocity between points must exceed 30 deg/sec. When 10 eye-tracking algorithms' accuracy at detecting saccades on a sample-by-sample basis (as we do here) was

compared, the IVT algorithm was second closest to human detection for saccade events[245]. An example of saccades and image is presented in Figure 4.1A.

The saccade's horizontal direction was determined by subtracting its ending point from the starting point. We coded the top left of an image as the origin, so if the saccade's ending point was less than the starting point (a negative value), it was considered leftward. In contrast, if it was positive, it was considered rightward (Figure 4.1B).

4.2.5 Analysis of electrophysiological data

Analyzing Saccade Onset Responses

Spike timestamps from offline sorted neurons were used to create binary spike trains. We then extracted 2-second epochs centred on each saccade onset for each of the sorted neurons. The spike trains were then binned into 50ms bins across trials (saccade events) to extract the instantaneous firing rate. Averages of the perisaccadic intervals (consisting of spike trains surrounding 400ms of saccade onset) were used to assess modulation (Figure 4.2A).

To determine the statistical significance of the maximum and minimum peri-saccadic firing rates, we used a nonparametric permutation method. More specifically, for each session, we extracted the same number of 400ms intervals (four example intervals in blue in Figure 4.2A) as the number of saccades in the session, only at random times. We then calculated the maximum and minimum average firing rates across these epochs for each neuron. By repeating this procedure 1000 times, we create a null distribution of average firing rates, drawn from the same window length as the perisaccadic window and the same number of events. These eight 50ms average firing rates were averaged to create a mean perisaccadic firing rate. If the actual mean perisaccadic firing rate for a given neuron exceeded the 97.5th percentile of the control null distributions, it was considered a significant perisaccadic increase. Similarly, if the actual mean perisaccadic firing rate for a given neuron was lower than the 2.5th percentile of the control null distribution, it was considered a significant perisaccadic decrease (Figure 4.2A).

As a result, neurons were classified into one of three groups – (1) non-modulated (no significant increase or decrease in firing rate during the perisaccadic interval), (2) perisaccadic increase (significant increase in firing rate during the perisaccadic interval), and (3) perisaccadic decrease (significant decrease in firing rate during the perisaccadic interval (Figure 4.2C). The multiunit activity (MUA) was calculated by averaging all modulated neurons' average firing rate aligned to saccade onset, separately for each category (decrease or increase). The percent change was calculated based on the ratio of the average firing rate per neuron during the saccade period, divided by the mean firing rate in the randomized control periods (Figure 4.2E). Then that percent change was averaged across neurons. We also calculated the perisaccadic firing probability density by fitting all spike timestamps in 2 seconds around each saccade with a kernel distribution with a bandwidth of 50ms. This probability density was then upsampled (using a bicubic spline interpolation) to obtain a 1ms resolution. The maxima and minima of this upsampled firing probability density were used to calculate the peak and trough latency of the firing rate increases and decreases, respectively, for the saccade-modulated units (Figure 4.2E insert). Histogram of the latencies are also presented in Appendix B Supplementary Figure 2C. Subsequent statistical tests on distributions based on these classifications were determined to be parametric (paired t-test, one sample t-tests) or nonparametric (Wilcoxon Signed-Rank Test or Wilcoxon Rank-Sum Test), based on the results of the Lilliefors normality test.

Although the interest in the present study focused on SU saccadic modulation of MTL structures, in two participants, we had the unique opportunity to simultaneously record activity from the occipital cortices (OCC). Therefore, we performed a unit-by-unit analysis from neurons acquired in this area, shown in the supplementary material, in a similar way as MTL neurons. A fourth classification was included for OCC: rebound modulation, consisting of an observed initial decrease followed by a sharp increase. We calculated the minima and maxima of the average firing rates in the 400ms perisaccadic window and compared these to randomly generated control null distributions of maximum and minimum average firing rates. If the maximum perisaccadic firing rate for a given neuron exceeded the 97.5th percentile of the control null distributions, and the minimum perisaccadic firing rate was lower than the 2.5th percentile of the control null distribution, it was considered a rebound (Figure S2C). No units from the MTL presented a characteristic rebound.

To determine if the amplitude of the post-saccade event-related potentials (ERPs)[216] were related to firing rate changes, post-saccade ERPs were computed from voltage traces of the most distal macroelectrode(i.e. the one closest to the corresponding microwires). Each macro electrode had a 200Hz lowpass filter and was downsampled to 1000Hz. A 60 Hz notch filter was applied to reduce environmental noise from the signal. Each macroelectrode ERP was then normalized by dividing by the standard deviation of the voltage trace of that electrode during the entire recording. The ERPs found to have a reversed polarity were flipped to obtain a positive waveform (MTL= 1/58; OCC= 5/8). We eliminated responses from electrodes with large artifacts in the ERP and, therefore, considered open or broken channels (MTL= 4/58; OCC= 0). The subsequent average from all electrodes was calculated and plotted for MTL (Figure 4.2F) and occipital electrodes (Appendix B Supplementary Figure S1G). The root mean squared (RMS) amplitude of the normalized ERP was then calculated from 10ms-510ms post saccade onset. This time was chosen as it is in line with the significant portions of the saccade ERP from our earlier work[216].

Previous LFP work has identified differences in responses based on direction of saccade relative to recording location[227] even as it relates to potential oculomotor artifact[247]. Therefore, we further labelled saccades as ipsiversive if the saccade's direction was towards the side of the recording electrode's hemisphere, or contraversive if the saccade's direction towards the opposite hemisphere. We repeated the categorization and ERP analyses described above, now separating events based on the saccade direction. Additionally, a paired t-test was used to compare ipsiversive to contraversive saccade RMS distributions. Finally, separating ipsiversive and contraversive saccades, we calculated the Spearman rank correlation between the ERP RMS amplitude and the percent change in firing (decreases only) of the corresponding modulated neurons close to those electrodes. Single unit modulation was similar across the MTL structures, so they were grouped together for further analysis (Appendix B Supplementary Figure 2).

Analyzing Image Onset Responses

Single unit responses to image onset were analyzed in a window between 200 and 1700ms after image onset, in line with previous single-unit literature[310]. Neurons were marked as modulated by image onset if their mean firing rate in this window significantly increased or decreased

compared to the corresponding null distribution (Figure 4.2A). Control null distributions for image onset analysis consisted of 1500 ms periods of spike trains at randomized timepoints. The MUA was also calculated for neurons which increased their firing rate to image onset (Appendix B Supplementary Figure 3).

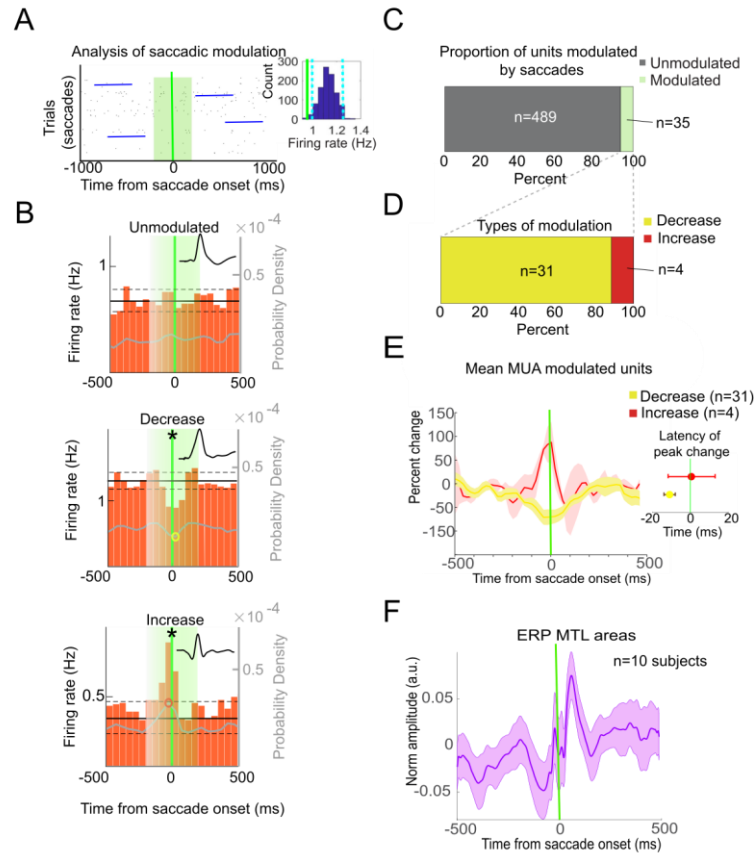


Figure 4.2| Categories and distribution of modulated units: A) The relationship between SEMs and SUA was investigated by comparing spike counts during the 400ms perisaccadic interval (green box) centred on saccade onset (green line) to those in control periods— bootstrapped aleatory 400ms epochs from each specific unit (blue lines). Insert: Null distribution of an example unit (dark blue). The green line represents the mean firing rate during the saccade period of the example neuron, and the cyan dotted lines 95% confidence intervals from the random time windows. The mean firing rate (green line) is left of the lower confidence limit (cyan line) and therefore demonstrates a significant average decrease in firing rate during the perisaccadic. Therefore, the unit is classified as "modulated"; B) Distribution of units modulated by saccades; C) Example of the different types of modulation observed. Modulated units were subdivided into

those that: i) decreased their firing rate and ii) increased their firing rate. Firing rate histograms of exemplary units and mean waveform of each unit. Yellow circle: decrease trough; Red: increase peak. Gray superimposed line indicates probability density (right y-axis) for visualization purposes. Only units with statistically significant firings during the perisaccadic periods (green box) were deemed to be modulated (asterisk); D) Distribution of the types of modulation observed; E) Mean MUA from modulated units in the MTL. Insert shows the latency of the peak change in firing rate from the MUA traces. There were no significant differences between latencies of units demonstrating an increase or decrease of firing; F) Mean ERP of electrodes in the MTL aligned to saccade onset.

4.3 Results

4.3.1 SUA within the MTL are modulated in the peri-saccadic interval

We recorded 524 neurons from MTL regions (hippocampus, amygdala and parahippocampal gyrus) across 11 patients. Table 1 shows the distribution of neurons analyzed from the different areas. Waveforms of some example neurons are shown in Figure 4.2C. In two participants, we had the unique opportunity to simultaneously record activity from the occipital lobe (Table 4.1, Appendix B Figure S1C). Overall, the various MTL structures presented similar results and were therefore grouped (Appendix B Figure S2). To determine whether saccades modulated single-unit activity in the MTL on a unit-by-unit basis, we analyzed the firing rate changes in a 400ms window surrounding each saccade and compared this activity to a matching null distribution generated by selecting random windows throughout the recording session (see Methods for details). In doing so, we found that 6.7% (35/524 neurons) of MTL neurons were strongly modulated by the saccade (Figure 4.2B). This is a somewhat lower percentage (~28%) than the other study looking at eye movements in humans[221]. However, factors such as saccade detection and modulation criteria differ between these studies[221]. When separating by direction (See Saccadic Modulation of the MTL is Directionally-Dependent), the proportion of modulated neurons found is in line with previous work with primates (20%)[268]. Interestingly, almost half of occipital lobe neurons were modulated around the time of saccades (464%, 58/125 neurons).

4.3.2 SEM related modulation is predominantly inhibitory

To determine how MTL SUA is modulated in the peri-saccade interval, we divided each unit into one of three categories: unmodulated, firing rate increase, or firing rate decrease. Of the saccade modulated units in the MTL, we found that the majority of units demonstrated a decrease in firing rate within the perisaccadic window (88.6% $n=31/35$), with the small remainder demonstrating increased firing rate (11.4%; $n=4$; Figure 4.2D).

To further interrogate this perisaccadic modulation, we classified the units into two groups based on their waveform width: broad-spiking (putative pyramidal cells) and narrow-spiking (putative interneurons). We found that of the small population of neurons that did increase their firing rates in the peri-saccadic window, a majority were the putative interneuron group of narrow spiking neurons (75%, 3/4) (Figure 4.3). In contrast, among the more prevalent group with decreased firing rates, most neurons were broad spiking (77.4%, $n=24/31$). The overall distribution of broad and narrow spiking units for MTL can be seen in Figure 4.3.

These findings suggest that saccades predominantly decrease the activity of putatively excitatory neurons and predominantly increase the activity of putatively inhibitory neurons.

In contrast, many neurons in occipital regions demonstrated a general decrease in firing rate, like the modulated MTL neurons (43.64%; $n=24/55$). A larger fraction demonstrated a characteristic rebound activation pattern in the perisaccadic window (56.36%; $n=31/55$), which consisted of a significant transient decrease in firing in the peri-saccadic window, followed by a sharp, significant increase (Appendix B Supplementary Figure S1C). Only a small subset of the modulated occipital lobe neurons demonstrated an increase in firing rate (5.45%, $n=3/55$) (Appendix B Supplementary Figure S1D). Similar to the modulated units in MTL structures, units in the occipital lobe that demonstrated firing rate increases were mostly narrow spiking (66.7%, $n=2/3$). Interestingly, the majority of the rebound-modulated neurons in the occipital lobe were narrow spiking (80.64%, $n=25/31$; Appendix B Supplementary Figure S1F). As with the MTL, the majority of occipital lobe neurons that decreased their firing rate were broad spiking (87.5%, $n = 21/24$).

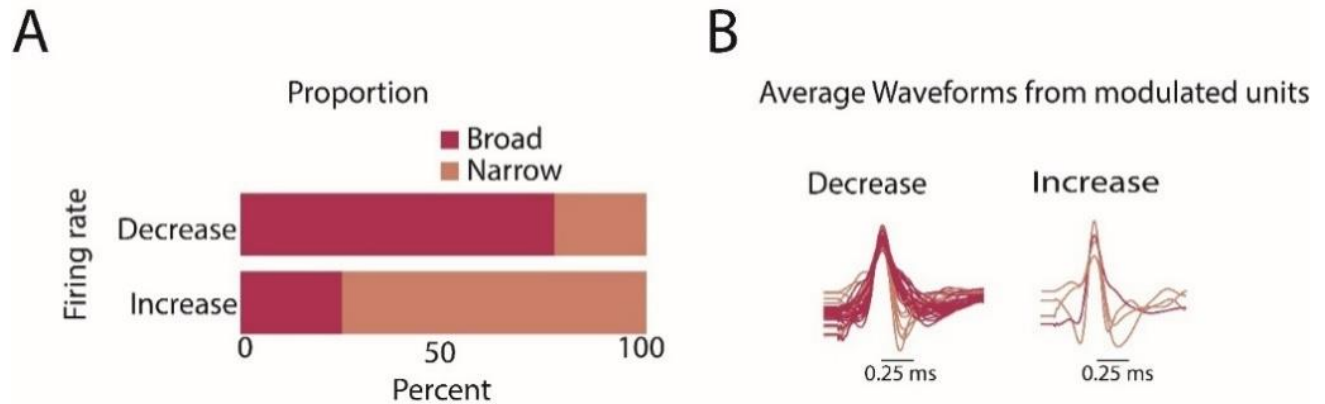


Figure 4.3| Broad spiking units largely demonstrate decreases in firing rate: A) Proportion of 'broad' and 'narrow' spiking separated by the type of firing rate changes observed in the perisaccadic interval. B) Average normalized waveforms from the MTL areas separated by type of firing rate change.

4.3.3 Saccadic modulation precedes SEM onset

Our previous finding that saccade-related ERPs are aligned to saccade onset rather than offset[216], as well as the contemporary understanding of the arrival time of CDs relative to saccade onset[299], together suggest SUA should be modulated before and/or during a saccade[299]. To investigate this, we separated the modulated units in the MTL by their modulation type (increase or decrease). We obtained the latency of the maximum average firing rate in a 400ms window surrounding saccade onset for units that up-modulated. Similarly, we found the latency of the minimum of the average firing rate in the same window for the units that were down-modulated. In doing so, we found that the trough of the firing rate decreases occurred at -11 ± 3 ms relative to saccade onset, whereas the peak of the firing rate increases occurred at 0.5 ± 12.57 ms relative to saccade onset (Figure 4.2E). Only down-modulated neurons were significantly different from zero (up-modulated, t-test $p=0.97$; down-modulated sign rank $p=0.001$) though these latency distributions were not different from each other (rank-sum, $p=0.33$). Because the perisaccadic modulation occurs before or during saccade initiation, well before the hippocampus would be expected to respond to changes in visual input, it is consistent with CD-like signals[302].

Similarly, in the occipital lobe, firing rate troughs and peaks occurred at $-11\text{ms} \pm 3.2\text{ms}$ and $0.33\text{ms} \pm 15.7\text{ms}$ relative to saccade onset. However, for units that demonstrated a rebound pattern, the rebound increase occurred at a longer latency ($27 \pm 3\text{ms}$; Appendix B Figure S1E). Thus, SEM-associated SUA modulation in both the MTL and occipital regions occur similarly before or during SEM, unlike image onset modulations of SUA that occur much later (see below and also[302]). In summary, that the perisaccadic modulation occurs before or during saccade initiation, well before the hippocampus would be expected to respond to changes in visual input, it is consistent with a CD-like modulation of MTL units[266].

4.3.4 The units and the response timing of the SEM-related SUA are distinct from those from image onset

The distinct nature of the ERPs associated with SEMs and image onsets[216] implies that the SUA associated with SEMs and image onset should also be separable. Specifically, ERPs associated with image onset were of an evoked nature, suggesting that we should observe increases in SUA instead of the inhibition-dominated changes in SUA associated with SEMs. Furthermore, the frequency components of the image onset evoked ERP were slower, and thus we would expect firing rate changes to occur later.

To explore these possibilities, we analyzed peri-image onset responses in a window of time between 200ms and 1700ms after image onset[310]. Neurons were classified as being modulated by image onset if their firing rate in this window significantly increased or decreased compared to the corresponding null distribution. We found that 13.7% of the recorded MTL units were modulated by image onset ($n = 72/524$; 67/524 increase; 5/524 decrease) (Figure 4.4B). This overall fraction is similar to that reported in previous studies[263], [301]–[303], [306].

Interestingly, we found the population of neurons modulated by image-onset to be distinct from those modulated around the time of SEMs (Figure 4.4C). Furthermore, image-onset modulated neurons demonstrated a peak increase in firing rate at $650 \pm 100\text{ms}$ after image onset, well after the saccade-related units. Thus, within the MTL, the units receiving visual information following image-onset appear distinct from those responding to saccade-related information. A greater

percentage of units in the occipital cortex than in the MTL were modulated following image onset (17.6%; n=22 /125) (Appendix B Figure S1H). Unlike the MTL, 4% (5/125 units) of occipital units were significantly modulated both following image presentation and during SEMs.

Taken together, these results demonstrate a clear dichotomy between SEM-related and image-onset unit activity in the MTL, where the former is dominated by inhibition, begins and ends earlier, and is mediated by a signal that modulates a unique set of neurons. The later feature of the SEM-related units in the MTL suggests that the modulating signals associated with SEMs within the MTL target distinct cell populations than units receiving visual input (Figure 4.4C).

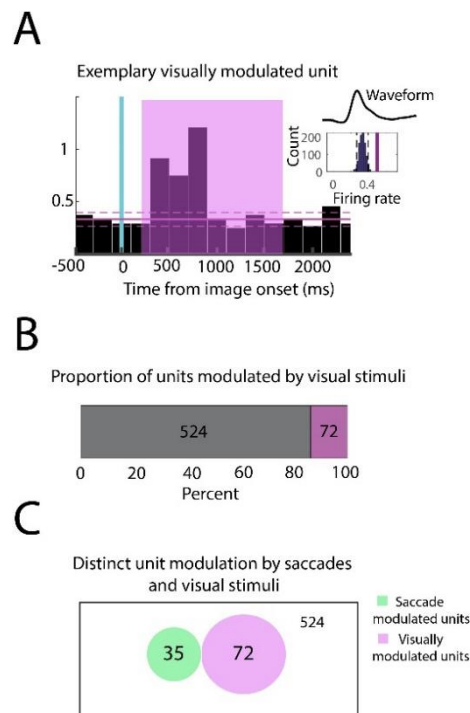


Figure 4.4| MTL units modulated following image onset are distinct from those modulated during SEMs: A) Histogram of an example unit modulated by image onset noted by the increase in firing rate starting 500ms after image onset (blue line). Insert shows the waveform and mean firing rate during the analysis period (200-1700ms); B) Proportion of units modulated by image onset; C) Venn diagram of visually modulated units (purple) or perisaccadic period (green). No intersection was found between the two populations of units, suggesting that units modulated by saccades are distinct from those visually modulated.

4.3.5 Saccadic Modulation of the MTL varies with saccade direction

In other SEM-related CD circuits, a CD signal conveys information regarding the ensuing saccade's direction and magnitude, likely facilitating anticipatory remapping of receptive fields in visual areas[269], [311]. Thus, we would expect that if a CD signal mediates the MTL firing rate modulation, we should observe directionally selective modulation in the peri-saccade interval. To investigate this question, we separated saccades into two groups, ipsiversive and contraversive (there were no significant differences between the number of saccades in these groups paired t-test $p=0.16$; Figure 4.1B). In addition to the 6.7% ($n=35/524$) of neurons that were classified as modulated when collapsing across saccade direction (Figure 4.2B), separating saccades into ipsi- and contraversive groups revealed a much larger fraction of modulated neurons (20.4%, $n=107/524$) (Figure 4.5B). In fact, most of the units that were modulated when analyzing all saccades (28/35) were also directionally modulated (i.e., modulated in one particular direction), suggesting that the previous categorization of SEM associated SUA modulation was masked by pooling together all the saccades. This finding provides strong evidence that saccadic modulation of neural activity in the mesial temporal lobe structures is directionally dependent.

To further characterize this directional modulation, we classified these effects as 1) Lateralized decreases (a decrease in firing rate, but only for ipsiversive OR contraversive saccades); 2) Lateralized increases (an increase in firing rate, but only for ipsiversive OR contraversive saccades); 3) Mixed (increased firing rate in one direction, and decreased firing rate in the opposite direction). In the MTL, most directionally modulated units fell into the lateralized decreases category ($n=73/107$), consistent with one of our main findings, that units are largely inhibited in the peri-saccadic interval. A smaller subset of units had mixed modulation (Figure 5B; $n= 23/107$). Only a small population of neurons presented lateralized increases ($n= 11/107$) (Appendix B Supplementary Figure 4A).

As before, our cell-type analysis revealed that the majority of MTL neurons that presented lateralized decreases in firing were excitatory broad-spiking (70%; $n=51/73$), while a majority of the neurons that presented a lateralized increase in firing were inhibitory narrow-spiking (64%

n=6/11). The majority of units presenting mixed directional effects were classified as "broad-spiking" (65.21%; n=15/23) (Appendix B Supplementary Figure 4B).

Additionally, we investigated the directional modulation of units in the occipital lobe. Here, 62/125 (49.6%) units were directionally modulated. Unlike the MTL, there was a smaller overlap between the directionally modulated units and those units modulated when collapsing across saccade direction (n = 25 units were common between both groups) (Appendix B Figure S11). Overall, there was significant directional modulation of single-unit activity in the occipital lobe, similar to that observed in the MTL.

4.3.6 SEM related SU firing rate decreases correlate to post-saccade ERP amplitude

In our previous work, we identified a short-latency, saccade-aligned phase-resetting ERP in the MTL LFP aligned to the saccade onset[216]. The combined observation that post-saccade ERPs align to saccade onset[216] and that SU firing rate changes are confined to the peri-saccade interval suggests that the SU firing rate changes drive the subsequent ERP. If this is so, then the amplitude of the SEM-related ERP should depend on the saccade's direction and be correlated to SU firing rate changes. To explore these possibilities, we calculated the saccade-aligned ERP for both ipsiversive and contraversive saccades (Figure 4.5C). We found that the RMS values 10-510ms after saccade onset (corresponding to the significant portions of the saccade ERP from our previous work) depended on saccade direction (Figure 4.5D). Specifically, the ipsiversive saccade ERP had a significantly greater RMS magnitude than the contraversive ERP (Ipsiversive = 0.09 ± 0.019 normalized amplitude; Contraversive = 0.04 ± 0.009 normalized amplitude; $p < 0.05$ Figure 4.5D). Thus, both the ERP and SU firing rate changes depend on the direction of the saccade.

Additionally, if the earlier peri-saccadic firing rate decreases underlie the generation of the later occurring post-saccade ERP, we would expect firing rate changes to be correlated to ERP amplitude. To explore this possible relationship, we measured firing rate decreases in the directionally modulated MTL units (contraversive or ipsiversive modulated unit and corresponding ERP (contraversive or ipsiversive ERP from electrode corresponding to the modulated unit) RMS amplitude for each patient. Spearman's rank correlation between these

measures revealed that firing rate decreases were positively correlated to ERP magnitude (Figure 5E). Thus, the more strongly BS neurons were inhibited – the cell-type that demonstrates the most consistent decrease in firing rate – the larger the ERP. We infer from this relationship that the post-saccade ERP[216] may be in fact a proxy for the strength of an earlier, largely inhibitory modulating signal (see Discussion).

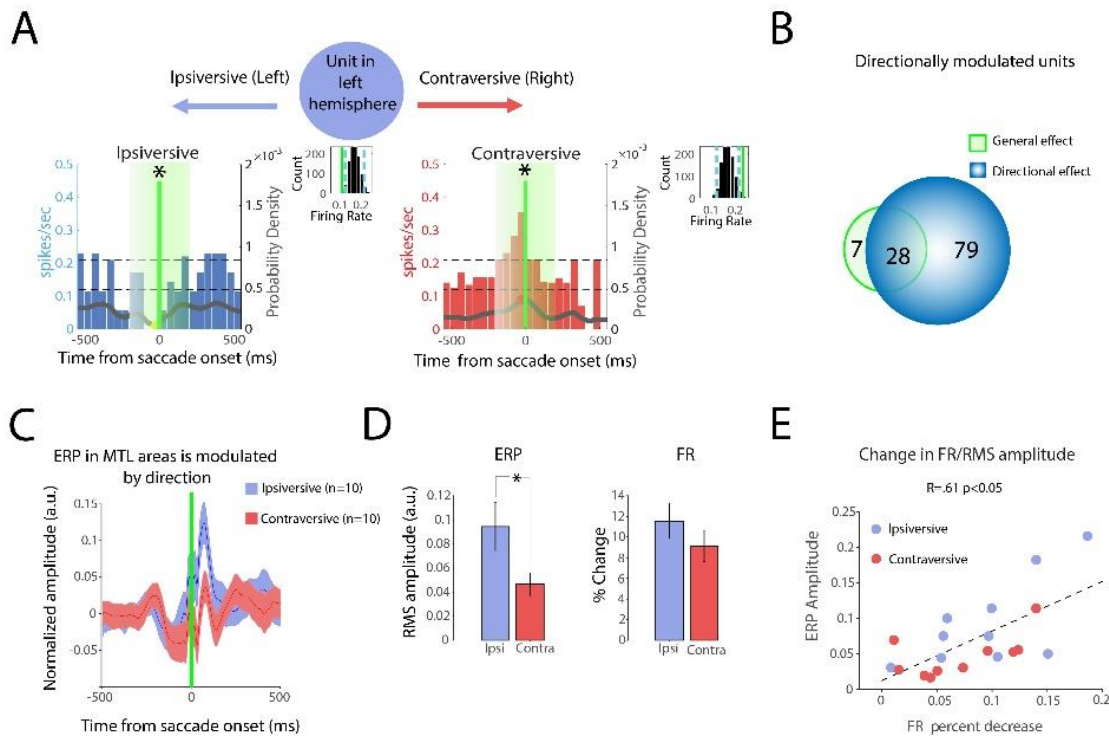


Figure 4.5| SEM-related SUA and ERPs are directionally modulated and correlated to one another: A) Ipsiversive and contraversive firing rate changes of an exemplary unit. Units were classified as "modulated by direction" if there was a significant increase or decrease associated with contraversive or ipsiversive saccades. The unit in this example shows a decrease in ipsiversive saccades and an increase in contraversive saccades. Insert shows the distribution of units during control periods and mean firing rate during the saccadic period (green line). B) Venn diagram showing the proportion of units modulated by saccades (green) and the units that showed a directional effect (blue). C) ERP from electrodes localized in the MTL associated with ipsi- and contraversive saccades. D) The left graph shows LFP RMS amplitude separated by the direction of the saccade. RMS amplitudes of ipsi- and contraversive ERPs are statistically significantly different. (* $p < 0.05$). The right graph shows the percentage modulation of units during the saccade period compared to randomized control periods. E) Correlation of LFP and unitary activity measurements showed in A, presenting a positive correlation.

4.4 Discussion

In our previous work[216], we presented LFP evidence that 1) the MTL is uniquely modulated around the time of SEMs as compared to image onset; 2) this modulation was consistent with a phase resetting response, and; 3) the alignment to saccade onset of this phase resetting was suggestive of a CD-like signal. These conclusions comported well with extensive NHP literature regarding the extra-retinal contributions to the modulation of LFPs in MTL and other visual areas[198], [199], [221], [224], [227], [266], [312]. Here we present six key findings derived from human SU recordings that greatly extend these findings, to provide a plausible mechanism by which extra-retinal signals that accompany SEMs, modulate the hippocampus and surrounding MTL structures in humans. Our six key findings are: (1) the peri-saccade interval is dominated by inhibition (firing rate decreases of BS units, firing rate increases of NS units); (2) SU activity was modulated largely before and during the saccade; (3) the modulation contained directional information; (4) distinct population of neurons are modulated by saccades and image onset, and saccade-related modulations occur much earlier; (5) saccades modulation of occipital SUA is distinct from MTL SUA modulation; (6) the amplitude of the post-saccade ERP is correlated to the magnitude of the firing rate decrease of BS units in the peri-saccadic interval. Through the manuscript, we grouped MTL results based on similar modulation patterns (Appendix B Supplementary Figure 2), suggesting a CD like signal is widely present within the MTL and thus likely generally relevant to mnemonic processes, albeit different structures having variable roles in memory[35] [313]. However given that the majority of units we observed within the MTL were from the hippocampus, and the extensive knowledge about hippocampal physiology and function, we focus our discussion specifically on hippocampal circuitry as an exemplar.

4.4.1 Firing-rate decreases dominate the peri-saccade period

The combination of increased NS and decreased BS firing rates suggests that the incoming saccade-related signal has a net inhibitory influence. We argue that this pattern is consistent with a general CD motif, in which motor-related signals excite local inhibitory interneurons, which then inhibit excitatory neurons[225], [291]. There are other possibilities. It could be argued that

decreases in BS activity arise from the reductions in afferent visual input during saccadic suppression[295]. Arguing against this possibility, however, BS firing rates change before afferent visual input would arrive in the MTL. Moreover, the accompanying increases in NS unit activity would be hard to explain with afferent reductions. Another possibility is direct inhibition through long-range GABAergic projections. However, the direction of the SUA modulation we observe makes this unlikely[314].

Observing this saccade-related inhibitory mechanism in single units sheds light on the post-saccade ERP that we[216] and others[198], [199], [221], [315] have characterized. Since inhibition alters the timing of ongoing spiking through a pause-rebound mechanism[278], pausing MTL circuits right before a saccade would orchestrate a synchronized period of heightened excitability following the saccade. And, because these MTL circuits are tuned to resonate at theta[238], these dynamics would align theta (3-8Hz) phase with the initiation of a saccade[216]. Notably, the resulting theta “phase-reset” need not reflect the modulation of ongoing oscillations – an important consideration because theta is not prominent in the primate hippocampus[213]–[215] and certainly not continuous like those in the rodent[200]. We also provided evidence linking SU inhibition to ERPs. Because larger inhibitory post-synaptic potentials increase the probability of consistently timed rebound spikes[278], greater saccade-related SU inhibition should drive larger ERPs. This relationship is precisely what we observed when correlating the two. Thus, by combining SU recordings with ERP analyses, we provided much needed insights into *how* saccadic eye movement could initiate theta phase resetting.

Beyond eye movements, such an inhibition governed hippocampal phase reset is well described in response to both alerting stimuli in rodents (auditory clicks, smell, touching)[187], [316], [317] and electrical stimulation of intrahippocampal pathways[186], [188], [318]. Considering these parallels, perhaps eye-movement plans act as an alerting signal, preparing the hippocampus for important new visual input. Indeed, hippocampal phase resetting temporally organizes LTP and LTD periods relative to the stimulus generating the reset[189]. Thus, saccades, along with a myriad of externally driven salience signals, may leverage a general mechanism – inhibition mediated phase resetting – to organize the encoding of new and important information. This link between active visual sensing and specific memory processes in mnemonic structures is

consistent with a large literature rife with evidence linking saccadic eye movements to memory strength (for review, see[160], [319], [320]).

4.4.2 SU activity reflects the early arrival of spatial and temporal parameters of ensuing eye movement.

We further evaluated two core CD properties: that they should occur before movement and contain spatial information about the ensuing movement[299]. We indeed found that MTL SUs were predominantly modulated in the pre-saccadic window. This comports well with our previous observation that MTL LFP modulation is aligned to saccade onset and not its termination (i.e., fixation)[216]. Both findings are consistent with the notion that MTL neurons are more modulated by the motor planning of saccades than the resulting change in visual input. We also found strong directional modulation in MTL SUA. So much so that collapsing across saccade direction drastically underestimated the proportion of saccade-modulated units (6.7% of all MTL units) as compared to separately analyzing ipsiversive and contraversive movements (20.4%). Moreover, we found that ipsiversive saccades were related to larger ERPs than contraversive in the MTL, consistent with previous research NHPs comparing temporal and occipital lobes[227]. In that study, the direction was also associated with significant differences in temporal lobe LFP but not occipital[227]. In our study, a vast majority of saccade-modulated MTL units were directionally modulated (107/114, 93.9%). Although directionally modulated units were also present in the occipital lobe, they represented a relatively smaller proportion of the total number of modulated occipital units (62/87, 71%). It has been suggested that the modulation of units directly receiving visual information reflects an exafference signal more than the CD signal[264]. Accordingly, our MTL findings may reflect the outcome of a more unadulterated CD, whereas the occipital lobe saccade modulation is likely the summed influence of a CD and visual reafference[227].

4.4.3 SU modulated with saccades are distinct from units responsive to image onset

Visually responsive neurons increased their firing rates long after saccade modulated neurons, with their firing rate peaking ~500ms after image presentation. SU also exclusively increased their response to image onset, consistent with an evoked response[216] and sharply contrasting

with the decreases in SUA associated with SEMs. Surprisingly, image onset and saccades modulated separate sets of MTL neurons, suggesting that the pathways mediating the effects, and their targets, are distinct. In the neocortex, modulating influences exert themselves in extra-granular layers while driving thalamic inputs exert their influences primarily in the granular layers[164]. Though it is hard to translate neocortical architectonics to the hippocampus, we conject that image onset responses reflect entorhinal inputs that excite neurons in the pyramidal layers[208]. In contrast, elucidating the source of the modulating CD signal, which excites interneurons, will require additional experiments.

For CD modulation to originate from motor structures (i.e., the superior colliculus), there must be anatomical connections between the oculomotor systems and the MTL. While there are no direct anatomical connections between these systems, indirect cortico-cortical connections may facilitate this type of communication. For instance, there are indirect connections between frontal eye fields (FEF) and hippocampus[165]. This network supports top-down attentional control and is partly responsible for generating voluntary eye movements. Other voluntary controllers of eye movements, such as the superior colliculus[321] and the pulvinar, may also indirectly influence MTL structures[322]. Another possible source of both directional information and inhibition within the hippocampus, is the nucleus reuniens which contains head direction neurons in rodents[323], appears to have a modulatory influence within the CA1 region mediated predominantly through inhibition[324], [325], and is a critical memory related node mediating communication between the hippocampus and the medial prefrontal cortex[326]. Recently, saccade direction cells have been demonstrated in the NHP[268] - another target for reuniens efferents[327].

4.4.4 Role of directional information in the MTL

How might a CD signal be utilized in the MTL? Rather than indiscriminately inhibiting BS units, our results suggest that the CD could inhibit (or excite) distinct MTL units depending on the associated saccade's direction. This spatial tuning is reminiscent of the spatial and directional information that MTL structures in rodents use to create maps of the physical world, or cognitive

maps more generally[328], [329]; place cells[328], grid cells[93], [330], and head direction cells[331] have been demonstrated in the MTL. Primates, by contrast, primarily explore their physical world with their eyes. It is, thus, unsurprising that spatial information about eye movements should be reflected in the primate MTL SUA[199], [268], [272], [298].

Here, we add to this literature by showing that this directionally tuned peri-saccadic modulation is primarily inhibitory, suggesting that its role may be akin to the well-accepted role of CDs in stabilizing visual perception[267], [297], [332]. Specifically, CDs are thought to “unite separate retinal images into a stable visual scene,” as was beautifully demonstrated in experiments that inactivate the CD while NHPs explore visual scenes[297]. The resulting alterations of visual perception provided early links between CD and perception. The neuronal mechanism underlying such a perceptual role for a CD was speculated to be akin to the anticipatory shifting of receptive fields in the lateral interparietal sulcus during saccadic eye movements [269]. Analogously, the directional information (i.e., the “path” in path integration) we identify in the human hippocampus could be used to stitch together sequentially sampled windows into a singular memory of a scene[152], [157], [290]. Perhaps this mechanism may even generalize to reflect the hippocampus' emerging role in encoding “conceptual maps”[329], [333]. Whether initiated by the traversal of visual or conceptual space, a targeted inhibitory-rebound mechanism could facilitate a construction from parts reminiscent of episodic memory semanticization[333], [334] through path integration.

4.4.5 Limitations of current work

If the peri-saccade modulation is solely a result of extra-retinal signals, it should persist in darkness. While the restrictions of our clinical setting precluded our test of this hypothesis, previous work with human and NHP suggests that both saccade-related ERPs and SUA modulation are observed in darkness and/or blank screens[221], [272], [271], [312] but see[199]. For example, in humans, rapid-eye movements in sleep and wakefulness generated both ERPs and SUA modulations in the peri-“saccade” period, interestingly with decreases in SU firing rates before the rapid eye movement with increases afterwards in all cases but awake non visual stimulation[14]. Their observed rebound pattern is reminiscent of the firing rate change we observed exclusively in occipital lobe units (Appendix B Supplementary Figure 1).

By contrast, a recent NHP study demonstrated no appreciable modulation in hippocampal MUA following saccades on a blank background, despite saccade-associated phase clustering in the LFP[312]. This analysis approach, however, averaged across all units, rather than focusing on the small proportion of modulated units, as we and others have done. Had this more sensitive approach been used, SUA modulation may have been observed while looking at a blank screen. Relatedly, our initial investigations only revealed phase clustering when exploring images, not during saccades on a dark screen [199]. However, these were based on saccades made during a blank screen inter-trial interval immediately following reward delivery, rather than longer periods of complete darkness outside the task regime, SU activity was not analyzed, and data from a single NHP subject was included. Thus, while there is some heterogeneity in the literature, a large body of work supports the hypothesis that saccadic modulation of activity in the MTL persists in the absence of visual input, further supporting the notion that this type of modulation arises from an extra-retinal signal.

4.5 Conclusion

In summary, we characterize SUA in MTL and occipital lobe structures to explore the hypothesis that an SEM-related CD-like signal exists in mnemonic structures of the human brain. Employing a unit-by-unit analysis of firing rate changes, we provide compelling evidence that SEMs are associated with a modulating influence characterized largely by inhibition and containing directional information. We show that saccade-related modulation of MTL units occurs earlier than image onset modulation and is more inhibitory and directionally tuned in the MTL than in the occipital lobe units. All these distinctions are consistent with MTL neurons receiving a saccade-related CD signal.

We hope that these discoveries inspire future work to investigate how a CD-like signal contributes to memory, ideally by interrupting the CD signal[297]. The next steps in this pursuit would involve elucidating the pathway by which CD-like signals reach MTL structures and, to understand the inhibitory influence of this pathway, the laminar profile of the SEM-related CD-like signal. Obtaining current source density profiles and associated SUA and MUA, for example, could help address whether the observed inhibition of BS units might arise from

Schaffer collateral-associated interneurons that inhibit pyramidal cells[335]. Beyond clarifying the circuitry mediating hippocampal saccadic modulation, such cell-type and circuit explorations could inform the exciting field of neuromodulation. To date, such studies have been limited to loss-of-function results following electrical stimulation of hippocampal structures (i.e. memory disruption[24], [25], [27]). A deeper understanding of how hippocampal circuitry is recruited during visual search may provide new avenues for cell-type and timing-specific approaches to neuroprosthetic devices for memory.

5 Stimulation Effects on Memory

The material in this chapter has been adapted from a publication in progress.

5.1 Introduction

Episodic memory allows us to capture and record our natural environment, enabling us to rapidly store personal events to be later reexperienced[336]. Humans primarily explore their environment using vision. Therefore, it is not surprising that vision and episodic memory seem to be intrinsically linked (for review, see[160], [319], [320]. Visual explorations like these involve rapid movement of the eyes between two different fixation points, also known as a saccade. Eye movements and memory processes seem to be naturally linked since free viewing of a stimulus leads to stronger memory formation than restricted[337] or even yoked/controlled viewing[156]. The number of fixations/saccades during encoding can be predictive memory for an item, whereby more fixations correlate with stronger subsequent memory over a single viewing for objects[154], scenes[338] or cumulative across multiple exposures[172]. More fixations are also better for correctly identifying purposefully similar lure stimuli[148]. Even shorter length saccades preceding region of interest can be correlated to memory formation[155]. The critical question – is why? Is it that these eye movements bring with them more information to build rich memories, reflect heightened states of arousal, or might they be linked to physiological states that promote memory formation?

Indeed, eye movements and episodic memory have been shown to rely on connected networks of brain regions. In particular, mesial temporal lobe (MTL) structures such as the hippocampi that are necessary for the formation of episodic memories – also influence how people visually explore their environments. Even without direct connections, eye movement and memory-based systems seem interconnected[165]. In fact, all hippocampal subregions except dentate gyrus have disynaptic connections to the frontal eye fields and/or superior colliculus[165] known to control the initiation of saccades.

Much of the work in eye movements and memory has looked at measurements like fMRI[166], [167], [338], effects of lesion/damage studies on eye movement[170]–[173] and memory or behavioural correlates of eye movement to memory[148], [154]. To investigate MTL structures at a temporal resolution of actual eye movements, intracranial electroencephalography (iEEG) can be used[195], [196], [339]. Saccades themselves generate a reliable event-related potential (ERP) with a distinct peak and trough in MTL structures[198], [199], [216], [221], [271].

The saccadic ERP does not just reflect an update in visual information but may reflect interactions between oculomotor and MTL regions since it persists even in darkness[221], [271] and has different characteristics than that of visual presentation for image onset [216]. ERPs can also be used to measure functional connectivity in the brain when recording their amplitudes in response to electrical stimulation of the brain. Regarding saccades, stimulation between memory and visuo-oculomotor structures exhibited a larger response when using stimulation post saccade compared with the same stimulation in the absence of saccade[179]. In the post-saccade ERP characterization, we and others have noted a phase reset in the theta(3-8 Hz) frequency band[198], [199], [216]. The well-established links between theta and memory in animals[340] and humans[341] could, thus, shed light on how saccade-related ERPs shape memory.

Specifically, theta has been proposed to resolve a long-standing challenge for memory formation: the brain must somehow juggle the relived past with the ever-evolving present. The SPEAR (Separate Phases of Encoding and Retrieval) model precisely proposes this separation that optimizes information flow. Specifically, it proposes a mechanism by which the hippocampus can encode memories during the trough of a theta rhythm and retrieve them during the peak²[204], [205]. Perhaps the saccade and its corresponding ERP might be ways to segregate such visual information flow through the hippocampus.

Kragel et al. (2020) recently used iEEG to link this theoretical work to human eye movements[196]. Specifically, they inferred periods of encoding and retrieval from memory-

² We will be using orientation from the hippocampal fissure which is 180 degrees out of phase when recording from statum radiatum in CA1[389]

guided eye movements. They found that theta phase coherence increased roughly 400ms before fixations on previously relevant locations (perhaps reflecting retrieval) and 100ms after fixating on a newly relevant location (perhaps reflecting encoding). Notably, phase coherence was concentrated at opposing phases: near the peak for retrieved locations and near the trough for new ones.

Further evidence that the theta phase can separate memory processes can be found in animal studies. Neurons in the CA1 subfield of the hippocampus fire at different theta phases in response to novel (encoding) vs repeated (retrieval) stimuli in rats [206]. This coordination is likely important for learning because applying electrical stimulation during the trough of theta induces long term potentiation (LTP)[121]–[123], [189] while the equivalent stimulation applied during the peak induces depotentiation (LTD) ;[121]–[123], [212]. LTP is predicated on the fact that “neurons that fire together wire together”[82] and involves the strengthening of connections for at least 1 hour[83]. The behavioural consequences of this timing have also been established. Rodents’ learning of conditioned stimuli was reduced when the stimuli were delivered during the phase of theta thought to be involved with retrieval[342]. In a more direct manipulation, hippocampal subregion CA1 was optogenetically inhibited in phase with theta; memory performance depended on whether the delivery was timed to occurring in the appropriate encoding or retrieval segment in a maze[202]. Such causal tests with direct manipulation based on theta phase are critical for mechanistic inferences.

Here, we directly manipulate the human hippocampus at these different theta phases during memory formation to assess its impact on human memory. We drew from an innovative procedure developed by McCartney et al. (2004). They utilized task-relevant events to reset the phase of hippocampal theta in order to time their electrical stimulation[189]. Specifically, they measured the average time to theta peak and trough following a light cue's presentation in a delayed non-match to sample task in rats. Following these calibration sessions, they applied high-frequency electrical stimulation at peak or trough times estimated from the calibration session ERP. They demonstrate that LTP was only elicited in response to trough stimulation.

Rather than a flash of light, we build off the approach and leverage the robust relationship between eye movements and hippocampal theta phase reset to causally assess how specific

phases of saccadic hippocampal ERPs relate to memory formation. We estimated the timing of the ERP peak and trough from ERPs computed from iEEG recordings in epilepsy patients. We first computed ERPs aligned to the saccade onsets during calibration sessions[216]. We then used real-time eye-tracking to synchronize hippocampal electrical stimulation with the estimated ERP peak, trough, or random times while participants visually explored natural scenes with embedded targets. Subsequently, we tested their ability to recognize each scene and recall the associated target to determine how the timing of stimulation during encoding influenced the strength of their memories.

Interestingly, we found that scene memory depended on the precise timing of hippocampal stimulation. Consistent with the bulk of hippocampal deep brain stimulation research, we found that randomly timed stimulation reliably impaired memory formation compared to an unstimulated sham protocol. By contrast, precisely stimulating at either the peak or trough of hippocampal theta left memory unimpaired. Importantly, memory was comparable across peak and trough conditions. Together, these results suggest that the human hippocampal theta also generates states that are particularly relevant for memory formation but not the differentiation of theta peaks and troughs.

5.2 Materials and Methods

5.2.1 Participants

Eighteen participants completed at least one session of the memory task while receiving deep brain stimulation (DBS). Of these participants, only 14 received stimulation to their hippocampus. Other stimulation locations included the amygdala, prefrontal cortex, and/or parahippocampal cortex. Here, we report on those who received hippocampal stimulation, the site of our primary question. All participants were implanted with Behnke Fried (AdTech, etc.) macroelectrodes to record intracranial electroencephalography (iEEG), with locations strictly determined by clinical considerations. Participants were undergoing clinical observations at the epilepsy monitoring unit at Toronto Western Hospital to localize epileptogenic regions (Table 1). All participants voluntarily provided written informed consent, and all research was performed in accordance with protocols approved by the University Health Network Research Ethics Board.

Table 5.1| Participant Summary table. This table separates participants by customization (Dark Grey) and the population average (Light Grey). Partial customization has no colour where * indicates the timing (peak or trough), customized based on the ERP. Including the location of stimulation electrodes, timing of stimulation and what sessions are completed. A, Anterior; HC, Hippocampus; L, Left; MTL, Mesial temporal lobe; P, Posterior; R, Right.

ID	Sex	Hand	Seizure Zone	Location	Cathode	Anode	Stim Peak Timing (ms)	Stim Trough Timing (ms)	Custom (Y/N/P)	Sessions (rec/targ model)	Level of Education	Age	Onset Age
1	M	R	RMTL	RPHC	HC	WM	149	236	Y	3(3/3)	Bachelor's Degree	26	14
				RAHC	HC	HC	149	236	Y	2(2/2)			
2	F	L	Right Frontal	LAHC	HC	HC	61	167	Y	3(3/3)	Associate Degree	45	12
12	M	R	Unknown	RAHC	HC	HC	57	170	Y	2(0/2)	Unknown	49	0-18
13	M	R	Diffuse	RAHC	HC	HC	212	316	Y	3(3/3)	High School	26	9
				RPHC	HC	HC	191	297	Y	2(2/2)			
14	F	R	Left MTL	LPHC	HC	HC	190	130	Y	3(1/0)	College	64	20
22	M	R	Left MTL	RAHC	HC	HC	71	139	Y	3(2/2)	Junior High	28	16
28	M	mixed	LMTL	LPHC	HC	WM	92	145	Y	3(3/3)	High School	28	13
3	M	R	Left Occipital	RAHC	HC	HC	50	260	N	3(3/3)	College	20	15
6	M	R	RHC, LMTL	RAHC	HC	HC	50	260	N	3(1/1)	12 th grade	27	7
7	F	R	LMTL and	RAHC	HC	HC	50	260	N	2(1/2)	12 th grade	58	14
9	F	R	LPL5.6	RAHC	HC	HC	50	260	N	3(1/3)	High School	46	14
10	F	R	Right insula	RAHC	HC	HC	50	260	N	3(2/0)	High School	20	6
				RPHC	HC	HC	50	260	N	3(2/2)			
14	F	R	Left MTL	LAHC	HC	HC	60	130	N	3(2/1)	College	64	20
14	F	R	Left MTL	LPHC	HC	HC	60	130*	P	3(0/0)	College	64	20

16	M	R	Left MTL	RAHC	HC	HC	78*	130	P	3(3/3)	Associate Degree	28	26
27	M	mixed	Right cortex	RAHC	HC	HC	78*	130	P	3(3/3)	High School	25	13
				RAHC	HC	HC	78*	130	P	3(3/3)			

5.2.2 Closed-Loop Deep Brain Stimulation System

We developed a pseudo-phased-based closed-loop DBS system to apply hippocampal stimulation based on the online detection of eye movements (Figure 5.2A). We used an EyeLink Portable Duo (SR Research Ltd., Osgoode, Canada), placed at the bottom of the experiment presentation laptop screen, to track eye position at 1000Hz. We used the EyeLink EDF Event Detector to pre-process eye position data and then identified saccades using the Identification by Velocity Threshold (IVT) algorithm (>30 deg/sec) on a sample-by-sample basis. The IVT was shown to be closest to human detection for saccade events[245]. Of note, we required more than 10ms of velocity data following saccade classification to minimize the chance of triggering stimulation off blinks, which are often initially misclassified as saccades. Once a saccade was detected, we sent a signal to the experiment presentation software (Presentation™, Neurobehavioral Systems), which then signalled our purpose-specific Arduino to trigger an Ojemann Grass Stimulator™. This stimulator then applied customized bi-polar hippocampal electrical stimulation through implanted macroelectrodes. In tandem, iEEG data was recorded using a 256-channel Neuralynx™ Atlas Data Acquisition System (Neuralynx Inc, Bozeman, MT) at a sampling rate of 32 kHz and subsampled to 4kHz with a high cut of 0.1Hz and low pass filter of 1000Hz. Neural and eye-tracking data were synchronized by sending TTL triggers from the experiment presentation computer to both the Neuralynx computer stimulator using a splitter.

5.2.2.1 Electrode Placement

Depth electrodes were placed stereotactically using either a Leksell frame or robotically (Neuromate). A 4-contact subgaleal electrode was used for ground and reference. This strip was placed over the parietal midline facing away from the brain. Electrode localization was performed by co-registering pre-op MRI with post-op CT using the iELVIS toolbox[246]. Only contacts that a neurosurgeon visually verified as being in the hippocampal body were used as the cathode for stimulation. Anode contact locations were restricted to the hippocampus or surrounding white matter (Table 1).

5.2.2.2 Stimulation Patterns and Customization

An “electrical stimulus” consisted of a train of five 0.1ms biphasic pulses separated by 2ms. We selected this pattern since when delivered at theta frequency[120] or to the peak of theta following a phase-reset[189], it optimally induces long-term potentiation[122], [123], [201]. During the experimental session, we applied four stimulation protocols as participants encoded information. Two protocols targeted saccade-locked ERP peaks and troughs, respectively. “Control” protocols consisted of sham stimulations (no stimulus) and random stimulation. In the random condition, we applied trains according to a uniform distribution. The total number of trains yoked to the participant’s saccade rate (rounded to the nearest second), ensuring that all stimulation conditions only vary in the timing of stimulation. We applied each of the stimulation protocols across a block of 10 trials within a session to reduce carry-over effects, counterbalancing the order across participants to reduce order effects. Post hoc, we performed Wilcoxon Ranked Sum Test to confirm that stimulation types did not differ in saccade and stimulation event counts (Figure 5.4).

In a calibration session before the main experiment, we customized two aspects of the electrical stimulus: the saccade-locked timing and the intensity (Figure 5.2B). Participants first received task instructions and then were given an extended practice session. They visually explored 40 scenes and then had their memory tested for all of them (see Memory Task details below). To calibrate the timing of saccade-locked theta peaks and troughs, we obtained a saccade initiation-locked event-related potential (ERP) for all grey matter electrodes from saccades made on the scene images. We then calculated the timing of statically significant maxima (peak) and minima (trough) using polarity permutation testing[343]. We identified electrodes in the hippocampus that showed a significant peak and trough and used these times to customize the stimulation timing in the main task (*Customized Participants*). Participants who did not show a significant ERP were stimulated with the average peak and trough timing of previously tested participants (*Non-Customized*). The average times (50ms and 260ms) for non-customized participants tested early in the experiment were based on saccade locked ERP timings from previous work[216]. After a sufficient sample was collected on the current protocol (n= 9), we replaced the average times with those derived in this task’s practice session (60 and 130ms).

We calibrated the intensity of stimulation with a novel cortico-cortical evoked potentials (CCEPs) approach. CCEPs index cortical connectivity[174], [176], [178], making them a powerful index of stimulation's downstream effect. We, thus, inferred that the minimum current required to elicit a CCEP in any grey matter electrode was sufficient to evoke presynaptic responses that propagated along axons. We began at 0.5mA of current for each stimulation site, increasing by steps of 0.5mA until a reliable CCEP was observed. For each current level, stimuli were delivered in a train based on the participant's average saccade rate (rounded to the nearest second) during the calibration session. This stimulation was delivered for 4 seconds with 2-second breaks to match our task timing. Stimulation intensity did not exceed 8mA[24] as a safety precaution, and we expected less than 3mA to be sufficient[128], [344]. We initially used 12 bursts of 5 pulses (Subject 1 and Subject 2). We switched to 36 bursts to ensure reliable ERPs at lower currents. The lowest current level that results in a significant CCEP identified with permutation testing[343] was used for closed-loop stimulation.

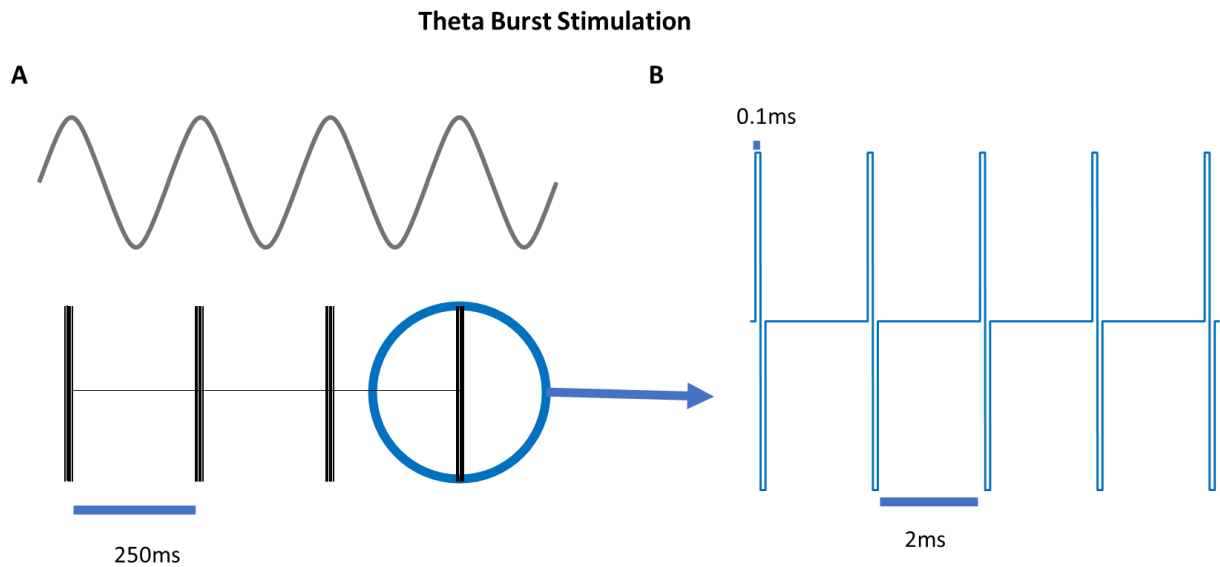


Figure 5.1| Example of theta-burst stimulation protocol: Parameters that can change across studies, including the pulse width, number of pulses per burst, frequency of stimulation pulses and how many bursts per second (i.e., targeted theta frequency). A) We see one cycle (1 second) of stimulation. B) Zoomed in version of the five pulses delivered in one burst. As evident here, theta burst stimulation entails delivering a high-frequency burst (depicted here as a 500Hz burst) in a theta envelope (depicted here as 4Hz). Typical

theta-burst protocols can have anywhere between 3-8 bursts per second, 200-500Hz bursts, 3-8 pulses per burst and a pulse width between 0.1-0.3ms.

5.2.3 Memory Task

We developed a memory task that encourages visual exploration during learning to test the effect of saccade-locked DBS on memory formation.

Stimuli and Apparatus: Images of conceptually distinct outdoor and indoor scenes were used as stimuli in the memory task. They were collected using Google image search and a database of scenes[345] standardized to 1400x1000 pixels. Four copies of a target image – either a cartoon bunny or coyote – were positioned within each of the scenes according to an updated version of the universal image quality index (UIQI; Wang and Bovik 2002) called the Structural Similarity Index (SSIM)[347]. The algorithm compares the target's similarity to each possible placement within the scene to find locations where it would be camouflaged, and UIQI has been shown to increase visual search times in camouflage[348].

The experiment was presented on a 15-inch laptop using Presentation software (NeuroBehavioral Systems, Albany, CA, USA). Participants were seated in their hospital beds, and the laptop was placed in front of them at a comfortable viewing distance. An infrared video-based eye tracker (EyeLink Duo; SR Research Ltd., Osgoode, Canada), connected to the laptop with ethernet, was used to monitor and record their eye movements throughout the task. All participants first underwent a 13-point eye-tracker calibration and 9-point validation test before starting each day of testing.

Procedure: Each memory task session consisted of a study and a retrieval phase. In the study phase, participants were presented with 40 scene images embedded with four copies of one of two possible targets (Figure 5.2C). Participants were instructed to visually search through the image to find as many of the targets as possible. They were also instructed to keep exploring the scene and elaborate on what the cartoon character would do in the scene if they found all four targets to increase the depth of their learning. Each image was presented for four seconds, after which participants reported how many targets they found. When it did not interfere with the quality of eye-tracking data, participants used a keyboard to make responses (27/59 sessions); otherwise, they responded verbally, and the experimenter pressed the corresponding key. Each

response was followed by a 1-second fixation cross and then the next image. To facilitate the building of associations between scene images and targets, each target was repeated for alternating blocks of 5 trials. Across participants, scene images were consistently paired with the same targets and were presented in the same order within a session. Hippocampal DBS was applied throughout the scene presentation periods according to one of the four stimulation types described above in the Stimulation Patterns and Customization section. Stimulus type was counterbalanced across participants, such that a particular stimulation type was similarly likely to be applied in each quartile of the study block and to each studied scene image.

Following the study session, participants were presented with instructions and the retrieval phase task. On each of 80 trials, participants were first presented with either a scene from the preceding study phase or a new, unstudied scene. Target images were not embedded in these scenes. Participants were first asked to indicate whether they recognized the scene from the studied set or if they thought it was new. They then rated their confidence in their recognition judgement on a scale from not sure (1) to very sure (4). Lastly, if they recognized the scene, they were asked to recall which target was embedded within it. This task was broken into blocks of three self-contained sessions. If time allowed, different stimulation locations (e.g., anterior or posterior hippocampus) were tested in a second block.

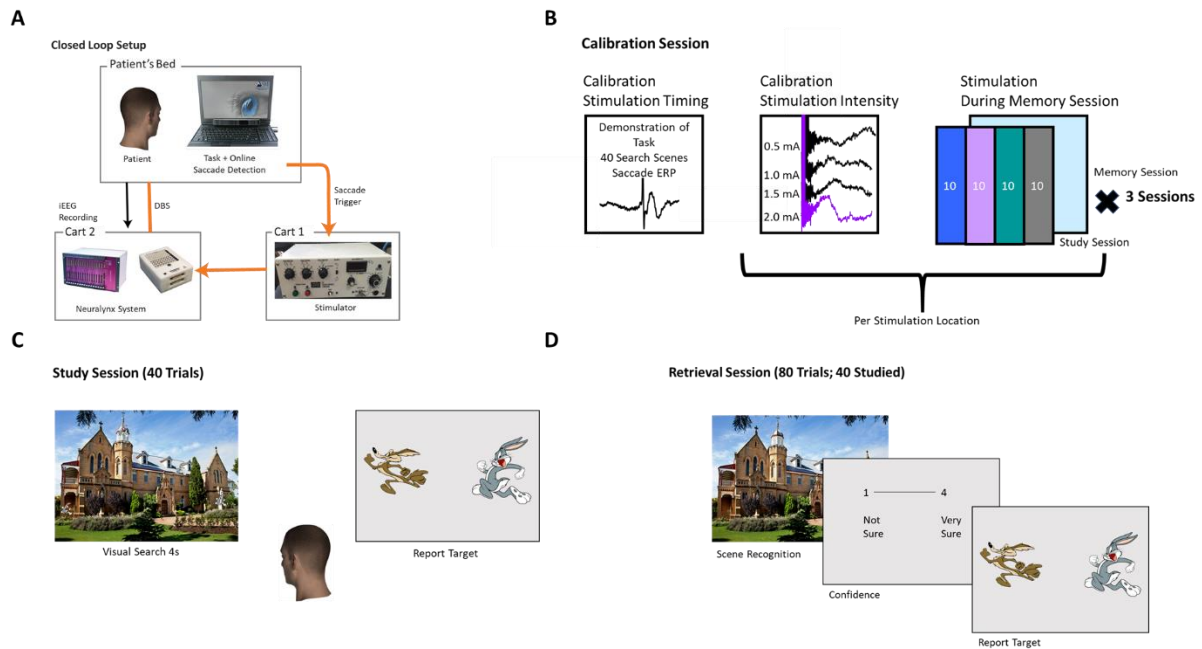


Figure 5.2| Behavioural task: A) Block diagram of the closed-loop stimulation set up in the patient room. B) Demonstration of the calibration of the task in extracting timing for the stimulation during a demonstration of the task, determining intensity that elicits a significant response in grey matter electrodes (significant current threshold in this example at 2.0mA) and shuffling of different stimulation types during each session of the task. C) Example study session with 40 unique scenes. D) Example study session with 80 scenes (40 novel 40 old), confidence and probe for the target.

5.2.4 Data Analysis

5.2.4.1 Behavioural Data Analysis

We used a generalized linear mixed-effect model (lme4 package in R programming language; [349]) to predict subsequent scene recognition (hit rate) and associative target memory accuracy on a trial-by-trial basis according to the trial's stimulation type. Such models are recommended to account for non-independence and incorporate random effects when dealing with intracranial brain stimulation and declarative memory [350]. We included a random slope for stimulation type and intercept grouped by participant. We incorporated data exclusion criteria to restrict analyses to sessions with reliable memory performance. For the scene recognition model, sessions were excluded if they had corrected recognition (hit rate – false alarm rate) scores lower than 0.25. One subject and seventeen sessions were excluded based on this criterion. We also removed trials with reaction time greater than 10 seconds. For the associative

memory model, sessions were further excluded if less than 15 old scenes were recognized, resulting in at least 15 target image judgements per session. Sixteen sessions were removed based on these criteria. Additionally, the target question was presented separately from the scene image. Since the scene was no longer visible, we excluded target memory for scenes when participants had not responded within 5 seconds.

To determine which factors moderate the impact of stimulation on memory, we included the interaction of stimulation type and location within the hippocampus (anterior/posterior), laterality (left/right), and timing customization in separate models. Only the customization of stimulation timing reliably interacted with stimulation type to predict subsequent memory, so our final recognition memory model for recognition:

$$\textit{Equation 1: Hit} \sim \textit{StimType} * \textit{Customized} + (\textit{StimType} // \textit{Subject})$$

5.2.4.2 iEEG Data Analysis

All electrophysiological data was pre-processed by downsampling each trial to 1kHz, bandpass filtering between 0.5 and 200Hz using a second-order Butterworth filter, and notch filtering at 60Hz to remove line noise. Notch filters were also incorporated at harmonics of 60 Hz up to 200Hz. All further analysis was performed using custom-written scripts in MATLAB (The Mathworks Inc, Natick, MA, USA).

To obtain ERPs for saccade or stimulation onset events, iEEG data from all trials and all relevant electrodes were aligned to the initial eye movement and electrical stimulation-onset and trimmed to epochs containing 1.2 seconds of data before and after each event. The ERP for each electrode was then obtained by taking the mean of these saccade-onset epochs across all trials from all experimental blocks.

To determine the statistical significance of each ERP, a representative distribution of ERP maxima and minima was obtained for each electrode/ERP using non-parametric permutation testing with randomized polarity inversions (3000 permutations). ERP values were deemed significant if they fell above the 97.5th percentile of the distribution of maxima or below the 2.5th percentile of the distribution of minima. This procedure was followed for both saccadic eye movement and stimulation-related ERP.

5.3 Results

During 59 sessions, we stimulated in 19 hippocampal locations (Figure 5.3A) across 14 participants. We leveraged the robust capacity of eye movements to elicit a hippocampal ERP[216] to stimulate different phases of the resulting ERP. We customized the timing of this stimulation to participant-specific ERP elicited by their eye movements if the ERP recorded from the stimulation contact showed a statistically significant peak and trough during the practice session (customized: 24/59 sessions; Figure 5.3B). For sessions where the corresponding peak or trough did not reach statistical significance, the population average peak and trough timing (Figure 5.3C) were used to time stimuli. The full breakdown of sessions is as followed: Fully non-customized: 20/59 sessions; peak only customized: 9/59 sessions; through only customized: 6/59. Examples of customized and non-customized responses can be seen in Figure 5.3B. To verify the timing of our customized stimulation, we extracted a saccade ERP from sham trials on all sessions for one participant – the trials with no stimulation artifact. Specifically, we visualized when stimulation would have been delivered with respect to such a saccade-locked ERP to indicate stimulation was seemingly aligned to peak and trough. As visualized in Figure 5.3D, the peak and trough times calibrated during the practice session remained aligned to the peak and trough of the sham stimulation saccade ERP (Peak in Blue and Trough in Pink Arrows, respectively).

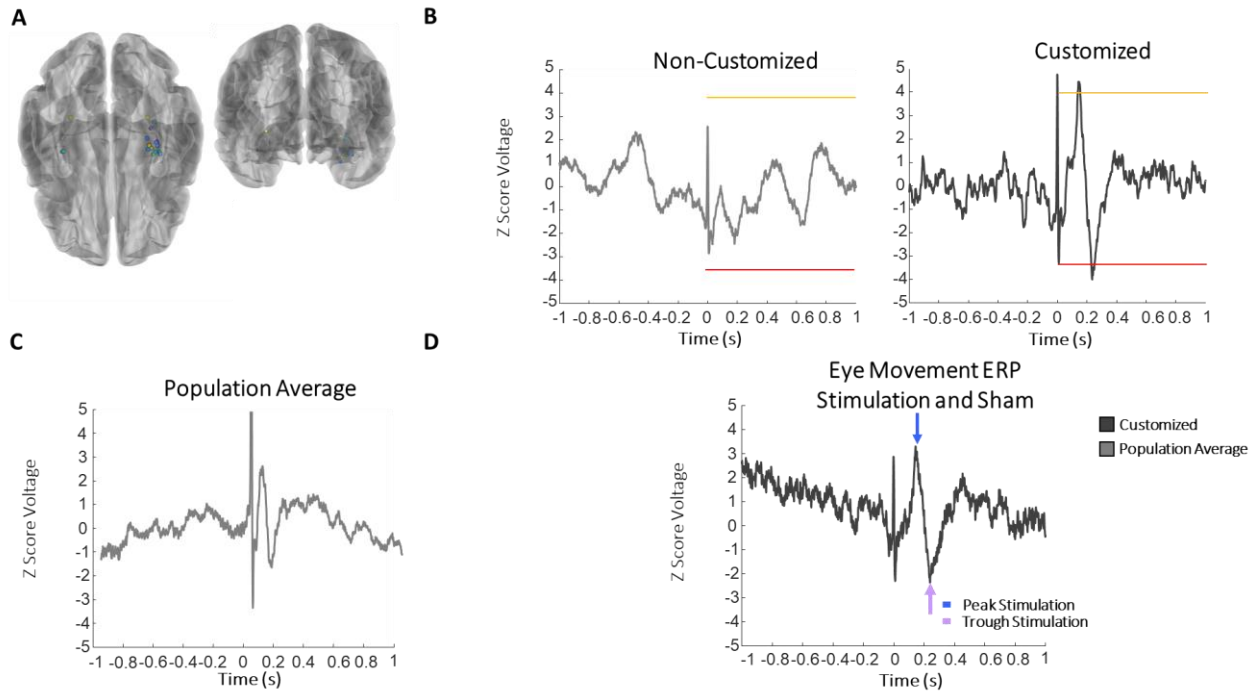


Figure 5.3| Extracting timing of stimulation: A) Demonstrates the location of the cathode for electrical stimulation. Each colour is a different hippocampal stimulation location B) Example saccade-locked ERP from Non-Customized and Customized timing participants. The yellow and red bars indicate thresholds for the significance of the response C) Timings used from population average ERP for non-customized subjects, significant peak and trough is from the average ERP from the demonstration of this task (60ms and 130ms respectively). D) Example customized participant saccade-locked ERP from sham trials. Arrows designate the timing of peak and trough stimulation calibrated during the practice session, demonstrating that the customized timing remained accurate throughout the stimulation sessions.

5.3.1 Eye movements and stimulation

We also confirmed that our stimulation protocols did not differ in their number of stimulation events or the number of saccades produced. Specifically, for the sessions incorporated in recognition analyses, Wilcoxon Rank Sum Pair tests revealed no significant difference in the rate of stimulation applied during peak as compared to the trough ($p=0.726$, median=1.20, $z=-0.350$) or random ($p=0.191$, median=11.23, $z=-1.307$), nor were there differences between random and trough ($p=0.127$, median=11.67, $z=-1.525$). Similarly, saccade rates did not differ during peak comparing with trough ($p=0.421$, median=3.10, $z=-0.804$), random ($p=0.100$, median=3.187, $z=-1.645$) or sham ($p=0.224$, median=5.245, $z=-1.216$) stimulation. Similarly, saccade rates did not differ between trough and random ($p=0.506$, median=1.017, $z=0.664$) or sham ($p=0.600$,

median=1.13, $z=-0.524$), and finally there was no significant difference between sham and random ($p=0.845$, median=-0.758, $z=-0.196$; See Figure 5.4).

5.3.2 Effect of Stimulation Types on Recognition

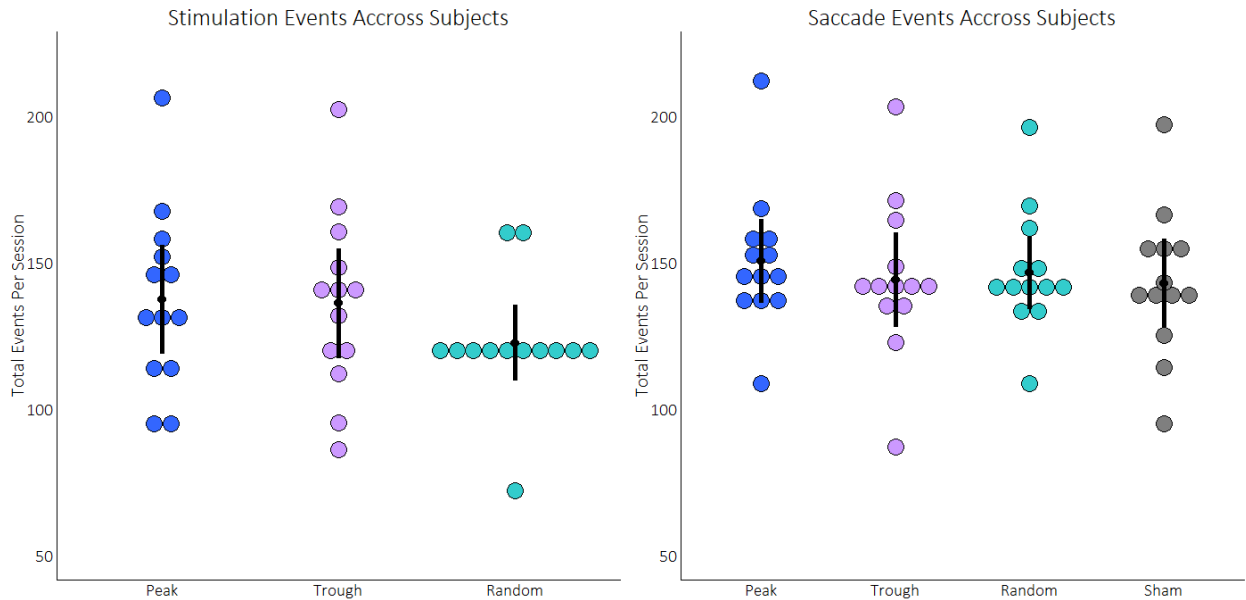


Figure 5.4| Stimulation and Saccade Event Distributions Based on Stimulation Type: Stimulation types did not significantly differ in the number of stimulation events administered per session or in the number of saccades produced. Dots indicate average rates per participant; black lines reflect the 95% confidence intervals.

5.3.3 Overall Memory Performance

Overall, 2360 images were shown across 4.21 ± 2.01 sessions performed by each participant. In the scene recognition task, an average of 62.5% (SE=5.8%) of old scenes were recognized (hits), and 22% (SE=5.5%) of new scenes were falsely endorsed as being studied (false alarms), leading to corrected recognition scores that were well above chance 0.404 (SE=0.054; $t=7.4$ df=13, $p<0.1*10^{-5}$). Associative memory performance was lower, with only 53.98% (SE=2.5%) of targets correctly recalled, though this trended to be above chance (50%, $t=1.6$, $p=0.067$). Non-customized and customized participants' memory performance did not significantly differ on sham trials when including all sessions for recognition memory ($z = -0.66$, $p=0.51$, $\beta=-0.28$, SE=0.41) or target memory ($z = 0.36$, $p=0.72$, $\beta=0.11$, SE=0.31).

5.3.4 Effect of stimulation types on memory across the group.

Across all 42 sessions (13 participants in the recognition model), stimulation appeared to be detrimental to recognition memory performance (Figure 5.5). Participants were less likely to later recognize scenes that were studied during peak ($z = -2.3, p=0.019, \beta=-0.47, SE=0.20$) stimulation, and random stimulation ($z = -3.9, p=0.0001, \beta=-0.73, SE=0.19$) as compared to sham. Trough stimulation did not result in a significant decrease in scene recognition but did have a trend ($z = -1.8, p=0.076, \beta=-0.45, SE=0.25$). Consistent with prior research[24], [25], [351], these results suggest that applying electrical stimulation to the hippocampus disrupts memory formation, regardless of its timing. By contrast, stimulation did not influence the likelihood of participants later being able to recall the associated cartoon character, with no difference when comparing sham stimulation to peak stimulation ($z=-0.82, p=0.42, \beta=-0.16, SE=0.19$), trough stimulation ($z=-0.19, p=0.85, \beta=-0.038, SE=0.20$), or to random stimulation ($z= 0.45, p=0.65, \beta=-0.08, SE=0.18$) (Figure 5.5). However, this lack of effect could reflect low statistical power as only a small number of trials and sessions were included in this analysis.



Figure 5.5| Group memory performance: Average hit rate (left) and target memory accuracy (right) for each stimulation condition when sham is used as a baseline. Dots indicate average rates per participant; black lines reflect the 95% confidence intervals.

5.3.5 Effect of timing customization on memory

We next determined whether each stimulation protocol's effect on recognition memory was moderated by the specificity of its timing, i.e., whether stimulation was delivered at customized peak and trough times or simply the populations' average times. Specifically, we included customization (fully non-customized vs. fully customized) and stimulation type and their interaction in one model predicting subsequent recognition memory. We did not analogously model associative memory because only a small number of sessions met our inclusion criteria. Much like the full sample, we found that stimulation generally impaired memory formation during non-customized sessions: people were less likely to later recognize scenes presented with peak ($z=-2.665$, $p=0.00723$, $\beta=-0.9327$, $SE=0.3497$) or random stimulation as compared to sham stimulation ($z=-3.0064$, $p=0.00723$, $\beta=-1.0936$, $SE=0.3570$), with a trend for the trough comparison ($z=-1.621$, $p=0.10502$, $\beta=-0.7551$, $SE=0.4653$). However, participants who received customized peak stimulation were more likely to later recognize scenes as compared to those whose peak stimulation was based on the population average ($z=2.200$, $p=0.02778$, $\beta=1.0218$, $SE=0.4640$). Figure 5.6 displays the results of this customization.

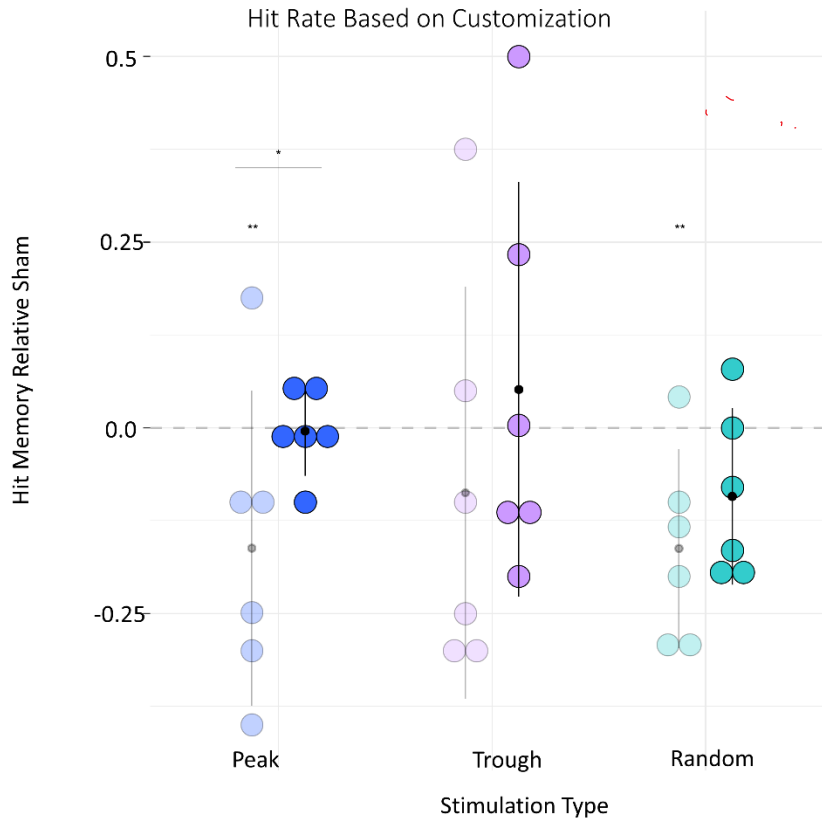


Figure 5.6| Customization effects on behavioural performance: Average hit rate population average (transparent) and customized (filled in) for each stimulation condition when sham is used as a baseline. Dots indicate average rates per participant; black lines reflect the 95% confidence intervals.

5.4 Discussion

Why does visual exploration improve memory formation[160]? Here, we explore the possibility that, by resetting the MTL theta phase[198], [199], [216], [312], eye movements create physiological states that are relevant for plasticity and memory formation[189]. To causally assess this idea, we performed saccade-contingent hippocampal DBS, targeting people's saccade-related ERP peak and trough. We found in this study that stimulation contingent on post-saccadic phase ERP impaired recognition memory. This stimulation did not alter the number of eye movements, suggesting behavioural effects were related to stimulation rather than impaired eye movements. Finally, we determined that memory could be recovered for customized phase stimulation to baseline performance when separating sessions based on customization.

Our findings in this study show generally, hippocampal stimulation at random times resulted in impairment of recognition memory. Such memory impairment to electrical stimulation is in line with previous work. Specifically, open-loop stimulation of the hippocampus can impair memory in recognition based tasks[24], [27]–[29] and recall[25], [30], [116], [117]. Interestingly, one study showed that hippocampal stimulation increased the formation of associative memories[26]. In contrast, our stimulation did not influence memory for scene-target associations. This result could be partly because a small sample size for target memory or overall performance was relatively low. Future work should consider ways to increase target memory performance.

We used two approaches to align stimulation times to saccade-locked ERPs. 24/59 of sessions had hippocampal electrodes exhibiting a significant ERP and received customized timing. We used average timings from our previous work to stimulate according to population averages to not miss this rare data collection opportunity. This approach seemed reasonable since our prior work showed robust ERPs when averaging across electrodes[216], suggesting that the timing was relatively consistent. However, we found an interaction between the customization approach and stimulation type, suggesting that precise timing critically determines the memory consequences. Specifically, behavioural performance could be recovered significantly for peak stimulation but not for the other stimulation timings. Notably, both groups had similar recognition performance in the sham condition, suggesting that the effect did not relate to pre-existing differences in memory abilities but was phase-specific.

The SPEAR model posits that the hippocampus engages in encoding and retrieval at specific theta phases[205]. Memory state specificity is evidenced by 1) differential inputs during the different phases of theta and 2) gamma frequencies embedded in distinct phases of theta[352]. Firstly the entorhinal cortex, the primary cortical input to the hippocampus, is thought to provide information about the external environment to area CA1 for encoding purposes. By contrast, retrieval of memories is believed to arise from the CA3 subfield of the hippocampus, supported by its dense recurrent connections. These processes seem to be biased at different phases of theta. In line with this, gamma oscillation(>50 Hz) seems to be involved with the entorhinal-CA1 network, and lower gamma (25-50Hz) seems to be involved with CA1-CA3 dynamics[353]. Fast gamma is seemingly involved with encoding, while slow gamma is apparently involved with retrieval, yet there are discrepancies in which phases they fall[209],

[210]. In this situation, if we are stimulating in customized individuals during the retrieval phase (peak) of theta, the impact may have little to no effect on memory since it is biased for retrieving stimuli. Therefore, it does not degrade with this stimulation and is similar to baseline.

Specific mechanisms for how such stimulation may impact memory are not fully understood. In this protocol, we implemented a pseudo-theta burst stimulation (TBS) protocol by stimulating contingent on eye movements since eye movements occur at a theta frequency. In an open loop fashion, TBS is believed to involve endogenous cellular mechanisms by mimicking in vivo firing in the hippocampus to elicit plasticity[120]. In prior work with humans, TBS has been used successfully in the entorhinal cortex[125], the amygdala[126] and fornix[14]. However, we found stimulation in this pseudo-TBS resulted in impairments.

One possible reason is TBS and other stimulation protocols have been recently shown to be primarily successful when targeting the white matter rather than the grey matter of the entorhinal cortex[118]. It was posited that this might be because stimulating gray matter may have a neural or disruptive effect on encoding introducing noise rather than a modulatory impact on the network. In our study, only 2/40 of distinct stimulation locations (anode and cathode) had the anode electrode in white matter. If the hippocampus is involved in encoding representation of objects, then perhaps generally stimulating may degrade memory[24], [25], [27]–[30], [116], [117].

There are a few limitations to consider in this study that could have impacted the results. Firstly, we are not detecting phase in real-time and only use a proxy for it based on a calibrated saccadic ERP. Some EEG and non-invasive stimulation techniques used to forecast phase to time stimulation have been researched[354]. Such techniques could be considered in invasive recordings. Perhaps this may elicit a stronger difference in phase-specific effects.

Also, given the nature of the study population, we are working with a small sample size and recording locations based on clinical needs creating variability within the data. For example, it has been suggested polarity reversal can exist depending on placement of recording contact in the hippocampus. Such timing effects may be confounded in our study due to this polarity reversal. In a recent eye-movement study with iEEG in humans, the hippocampal contacts interpreted their results, as we do -- as though all electrodes were recording from the

hippocampal fissure[196]. It is important to note that in our most recent work, we did not find such a shift in any electrodes for saccade ERP in which population timings were obtained[216]. Also, in the current study, the peak preceded the trough for all but one subject out of the customized subjects.

With regards to stimulation protocol parameters such as intensity, burst frequency and pulse width could have had an effect. Each subject's current intensity was personalized to elicit a reliable CCEP in another recording electrode as with other work using discharge thresholds [12], [25], [30], [118] but still introduces variability in the data. Our study used a 500Hz burst to ensure it fell as close to peak or trough as possible, faster than the 100-200Hz typically used in TBS protocols[14], [125], [127]. Stimulation pulse width is also an important parameter to consider. Action potentials based on stimulation are primarily incurred in axons using pulse widths of 30–200 μ s for large myelinated fibres and 200–700 μ s for small myelinated fibres[355]. Here, 100 μ s pulse-width was incorporated from some of our previous work in stimulation[344] and TBS in the fornix[14]. In many other TBS protocols, at least 200 μ s has been used[125], [127]. We did see a memory effect with this 100 μ s pulse width as well as significant CCEP however, stimulation at longer pulse width could be considered.

In the broader context, DBS can be used to interrogate mechanisms described here, but it can also be used for various neurological disorders[356]. Such stimulation can allow for investigating neural mechanisms by the nature of being able to turn off and on the delivery of stimulation at various times and analyzing both electrophysiological correlates and behavioural outcomes[25], [116], [117]. With some initial successes[12], overall, largely open-loop stimulation has resulted in impairment in memory[24], [25], [351]. Recent attempts have demonstrated success to improve memory by optimizing stimulation parameters, whether it be through changing the task[26], changing the stimulation pattern to theta burst[125], or using closed-loop stimulation[144], [147]. Stimulation timing in closed-loop has been investigated regarding delivery based on the ongoing frequency of oscillation[144] or single-unit activity[147]. The eye movement stimulation protocol presented here provides another potential insight into possible parameters for stimulation to alleviate symptoms in neurological disorders.

5.5 Conclusion

Our findings suggest that DBS, in a phase-specific matter, enables further exploration of the mechanism of memory formation. Specifically, we can modulate learning and memory performance in humans and investigate the causal mechanism of memory formation and their relationships to theta phase. Although our stimulation resulted in impairment, it suggests that with customized timing and perhaps more optimization of parameters, we can continue to learn about memory formation in a safe, controlled manner to improve memory moving forwards. Previous studies in deep brain stimulation have demonstrated the importance of both timing and location. Further understanding will be relevant for the development of neuromodulation techniques to improve memory. Our results indicate that stimulation in the hippocampus can have varying effects on recognition vs associated memory and customization based on phase-reset-based timings.

6 Discussion

The ageing population, Alzheimer's and Dementia are major issues facing Canada and the world. Treatments currently are not effective, suggesting the need for alternative options. DBS is a potential tool for augmenting memory against such neurological disorders. In our work, we explore the use of such stimulation to investigate memory formation mechanisms and develop stimulation practices based on the results moving forwards.

Previous studies have shown the interconnectedness between the memory and oculomotor systems. Additionally, DBS has been used in clinical[357] and research studies[358] to augment memory formation with mixed results. Typically, stimulation has been delivered in an open-loop or conditional open-loop manner agnostic to the underlying neural activity. Recent studies have shown success with closed-loop deep brain stimulation, contingent on the ongoing brain activity.

One well-researched timing mechanism in the brain is a phase reset. Therefore, we hypothesized that if we could find a naturally occurring phase reset in the MTL, we could investigate the mechanism of memory formation and efficacy of stimulation in a physiologically relevant manner. Through this approach, we could develop additional avenues for the application of stimulation to modulate memory.

Our results demonstrate that timing customization can affect memory, although we did not observe improvements. Many neurological disorders include memory effects, and it creates the opportunity for further work in DBS contingent on phase reset from eye movements. Other non-invasive stimulation techniques exist that could, in theory, utilize this mechanism for various neurological disorders. The results from this work provide a framework to develop other stimulation techniques based on eye movements.

6.1 Saccadic Modulation as Timing in The Hippocampus

Any closed-loop DBS system requires a timing mechanism by which to determine when to stimulate. Previous work has used network connectivity power[144] or single unit communication in the hippocampus[359] to time stimulation. This thesis focused on utilizing the

phase reset-based system to stimulate at the subsequent peak and trough. Phase reset occurs naturally through afferent projections to the hippocampus[317], in response to stimuli such as tail pinching[122], light[189], and in humans has also been suggested in visual memory tasks through image onset[360] and eye movements[199].

To disentangle which stimulus elicited a phase reset, we first utilized a behavioural paradigm that combines image presentation and visual search to investigate which response is most like a phase reset or corollary discharge(CD) in the MTL structures. This signal was analyzed through both local field potential recordings and single-unit recordings from consenting epilepsy patients to evaluate how saccadic eye movements modulate activity in memory-related structures in the human brain.

6.1.1 Phase Reset through Local Field Potential (LFP)

iEEG responses are consistently analyzed in the MTL during visual memory tasks. Specifically, the ongoing iEEG recording or local field potential can be averaged aligned to stimulus onsets to look at differences between items remembered or forgotten. Various features of the MTL responses to image presentation (i.e. power, phase) have been shown to be strongly correlated to subsequent memory effects[137], [138], [190]–[192], [194], [217], [361]. Similarly, memory performance is correlated to aspects of eye movements (i.e. the more one explores a visual stimulus, the more likely they will remember it)[148], [150], [154], [155], [220], and the MTL responses associated with these eye movements have also recently been investigated[195], [196], [199], [221].

Behavioural paradigms utilizing visual stimuli elicit electrophysiological responses to both image onset and saccadic eye movements, which have resulted in a phase reset to both stimuli. It is essential to differentiate the MTL response to these different stimuli. Therefore, interpretations of what spectral features of a response characterize the neural correlate of a specific brain structure need to be made using electrophysiological signatures for both responses.

We utilized a previously reported behavioural paradigm on a new set of participants that incorporates image onset and saccadic search and is MTL dependent[199], [243]. Specifically, we demonstrated that response to eye movements were starkly and mechanistically different than

image onset. In fact, the eye movement response resulted from a phase reset, whereas the image onset response resulted from an evoked response.

Interestingly, the ERP as a result of eye movement was aligned to eye movement onset rather than the termination of eye movement in a fixation. The timing of the ERP response in the MTL was faster than visual information could travel to the hippocampus. Such a response opened the possibility that this signal in the MTL might result from an internally generated preparatory movement, known as a CD.

Of note, this finding is not necessarily just relevant for timing stimulation effectively to eye movements. CD circuits have been found regarding impending movements for stabilizing the visual field but have not necessarily been as probed in mnemonic structures. Therefore, further work into cellular mechanisms is relevant to explore further whether this eye movement can be attributed to a CD.

6.1.2 Corollary Discharge through Single Unit Activity

Once we had determined that eye movement resulted in a phase reset, we wished to further probe this eye movement response mechanism in MTL structures. Single unit recordings provide increased spatial and temporal resolution compared to local field potential recordings. Thus, we could utilize these recordings to observe neuronal modulation at the level of individual neurons directly. We found that saccades modulate the activity of individual neurons in occipital structures and the MTL. Furthermore, we demonstrated that this saccadic modulation (1) varies depending on cortical location, (2) is starkly different from visually evoked modulation, (3) contains some directional information, and (4) largely results in neuronal inhibition in mesial temporal lobe structures.

While CDs are present throughout the motor system, they are best understood in the visual and oculomotor systems, providing internal information about eye movements. Various visuo-sensory regions of the brain use this information to stabilize visual percepts as our eyes ballistically saccade from one fixation point to another. In 2008, Sommer and Wurtz proposed simple yet powerful criteria for identifying such a CD[267]. In these criteria, they suggested that for a neuronal modulation to be a CD, (1) it must originate from a brain region known to be involved in movement generation but must travel away from the muscles, (2) it must occur just

before the movement onset and represent its spatial and temporal parameters, (3) it should not contribute to moving, (i.e. silencing the pathway should not affect movements), and (4) disturbing the CD pathway should result in disruption on the performance of a task that depends on the CD. While we developed supplemental criteria in our work, it is also important to consider our results in this broader CD literature.

Criteria 1

We found that the neurons modulated by eye movements in the MTL are entirely distinct from the population of neurons modulated by passive image presentation. This finding occurs in line with the previous LFP work that MTL response to eye movements is drastically different from the MTL response to image presentation[216]. Furthermore, our previous work, in which we observed saccadic modulation in the MTL using local field potentials, demonstrated that this saccadic modulation is aligned to the onset of movement (i.e. saccade), and not its termination (i.e. fixation). That alignment suggests that the response is generated by mechanisms associated with initiating the action, not in response to the visual input received upon its termination.

While we could not directly test this hypothesis in our clinical setting, previous work with non-human primates (NHP) provides some meaningful insights. Various studies have shown that peri-saccadic modulation of single-unit activity[221], [272] and local field potentials[271], [312] persists in MTL structures, even in the dark (or on a blank screen).

For the observed MTL saccadic modulation to originate from motor structures (i.e. the superior colliculus), there must be some anatomical connections between the oculomotor systems and the MTL. While there are no direct anatomical connections between these systems, indirect cortico-cortical connections may facilitate this type of communication. For instance, there are indirect connections between frontal eye fields (FEF) of the dorsolateral prefrontal cortex (dlPFC). This network supports top-down attentional control and is partly responsible for generating voluntary eye movements and the hippocampus[165]. Other voluntary controllers of eye movements, such as the superior colliculus[321] and the pulvinar, may also indirectly integrate within the hippocampus[322]. The hippocampus has also been hypothesized to be at the top of the hierarchy of the ventral and dorsal visual systems (which include the oculomotor network)[362] as well as an integrator of neocortical information[363]. The hippocampus is also a large part of

the transformation of episodic memory trace or engram between the neocortex and the hippocampus in the component process framework model[364].

Criteria 2

The second criteria for a CD are that it should occur before movement and represent spatial and temporal patterns of the movement itself. MTL units primarily decreased firing in the peri-saccadic window. A phase reset of MTL is elicited mainly by inhibition or silencing of activity[273], [317], [318], [365]. We separated eye movements into ipsiversive and contraversive saccades and analyzed the single-unit modulation in response to these movements separately. Fascinatingly, we found populations of neurons that responded differently to saccades in different directions.

Criteria 3 and Criteria 4

For a signal to be a corollary discharge, it must not contribute directly to the movement, and disrupting it should affect the performance of the task that depends on the CD. We were not able to directly interrogate this during this task. However, Sobotka and colleagues previously delivered electrical stimulation to MTL structures. They found that post-saccadic stimulation enhanced the locally recorded evoked potential, but did not disrupt the ensuing eye movements, providing evidence that disrupting the saccadic modulation does not affect the actual movement[179].

We feel that through both the LFP and single-unit activity, we showed that eye movement could result in a theta phase reset or even corollary discharge. These are considered timing mechanisms for the brain in terms of plasticity or preparing the system based on an internally generated movement. This contribution to the literature provides an opportunity to investigate the circuitry and pathways initiating the CD signal. Probing CD circuits has resulted in better understandings of perceptions and, in this case, could potentially assist in the knowledge of memory. With a better understanding of memory formation and its structures, we can use external electrical stimulation more effectively.

6.2 Stimulation Contingent on Eye Movements and Theta Phase Reset

6.2.1 Saccadic ERP Based stimulation

Given that we were able to determine that the eye movement phase reset resulted in a potential timing cue in the hippocampus, we could investigate subsequent contingent stimulation. The SPEAR model suggested that the resulting phase of trough and peak from the resulting ERP would be biased to encode and retrieve the stimulus, respectively. Therefore, based on previous research demonstrating the importance of theta and phase-based stimulation, we hypothesized that such phase-based customized stimulation would elicit memory effects.

We assembled a closed-loop brain stimulation system that would detect eye movements from an eye tracker. Subsequently, we would find the saccadic ERP for each participant through a calibration session to determine if we could customize stimulation timings to peak and trough for that patient or use population timings.

The system was tested using hippocampal stimulation in 14 participants in a behavioural task testing both recognition for a scene and a target paired with it. We demonstrated that stimulation impaired memory for recognition of a scene while leaving target memory intact. However, when separating by customization, memory performance was recovered for those with customized timings in peak stimulation.

One of the main limitations in this setup is that we could not find a significant ERP in some participants. In those situations, memory was impaired across all stimulation types. Perhaps stimulation could be optimized per participant in timing and other stimulation parameters. Also, stimulation was delivered pseudo-closed loop since the ERP was determined based on a calibration session. In one subject, we were able to show that this stimulation occurred at similar timing during the saccadic ERP in the stimulation session, but there is still no guarantee. Even so, this saccadic ERP, theta reset timing provides the opportunity for further investigation into this field, specifically the interactions of such theta-based stimulation.

6.3 Findings Fit Within Literature on Theta

6.3.1 Theta and Memory

The theta frequency band has been consistently connected to memory. Neuronal firing within theta has been explored related to sequencing memory and spatial exploration in rodents (for review, see[366]. Studies have shown that spiking of neural activity in the hippocampus is significantly modulated by the phase of the ongoing theta oscillations, known as phase precession. Such precession has been demonstrated in both rodents[367] and humans[368] in spatial exploration and even in rodents as it relates to goals in a task[369]. Thus, the same anatomic MTL structures where neurons encode space also encode for memories. Such spatial firing has also been demonstrated during virtual navigation in humans identifying place cells[370], [371] and grid-like behaviour[93], [372].

Recently it has been found that theta phase-specific firing is not present in just phase precession but that neuron fire to theta phase in the hippocampus stronger when memories are formed[143], and in fact, neurons across the brain fire preferentially to theta phase in the hippocampus[373]. This suggests that the phase of the ongoing theta rhythm is critical to ongoing processes and is very sensitive to the timing of the phase. Such timing sensitivity is of particular note since the stimulation burst lasted 10ms, and customized timings could be only slightly different from population average timings.

In both studies investigating the mechanism of the visual response in the MTL, we found that image onset and eye movement activities occurred at different latencies in both the ERP and neuronal firing. Eye movements incurred theta frequency phase reset in the ongoing oscillations[216], while image onset occurred with power increase in many frequencies, including lower delta. Perhaps this variability in the temporal latencies of the two responses is related to varying brain states.

6.3.2 Brain States

Schroeder suggests that the brain can operate in two modes: a continuous/vigilant mode ready to respond to random stimuli and; an active sensing/rhythmic mode in which cortical oscillations are entrained to rhythmic stimuli[242]. Corbetta and Shulman suggest two similar modes along the visual path; (1) a stimulus-control mode where stimulus-driven control is supported by the temporal-parietal junction and the ventral frontoparietal network, and (2) a top-down, attentional-control mode which is supported by dorsal frontoparietal networks. In these models, the driving response of a sensory stimulus in its primary sensory area (visual stimulus in the striate cortex, or auditory stimulus in the auditory cortex) can be attentionally modulated by a secondary stimuli (sensory or internally generated) through a multi-frequency phase reset[374]. This modulation or supra-modal control can facilitate multi-sensory interaction to optimally encode the primary stimulus. Schroeder suggests that such supra-modal control operates by modulating the timing of oscillations and not by engaging new neuronal assemblies[374]. Recently, Marcin et al. proposed the Active Visual Sensing where the local neural response to visual samples reflects an interaction between retinal “driving” inputs and “modulatory” non-retinal signals[375]. Our single-unit response demonstrated two different modulatory effects. Saccade-modulated occipital units primarily increased firing in the peri-saccadic interval, whereas MTL units primarily decreased their firing.

One might consider the MTL to be the *primary sensory area* for memory, *driven* by stimulus-specific responses. In this case, from our previous work, image-onset serves as a visual stimulus that causes an evoked response in the MTL, associated with a post-stimulus power increase[216]. We saw an increase in post-stimulus firing in image-onset selective neurons in the MTL. On the other hand, eye movements can be considered supra-modal control signals that can modulate the phase of MTL activity to better encode the stimulus into memory. In this case, the saccade-onset response (which likely corresponds to the action of a saccadic efference copy) triggers a phase reset of the ongoing MTL activity by transiently inhibiting local neuronal populations[273], [317], [318], [365]. This may align the high excitability phase of the MTL oscillation with the incoming visual stimuli at the end of the saccade[204]. A recent study in NHP V1 has demonstrated that saccades are modulatory regardless of context delivery[376].

Ringo et al. suggested in 1994 that saccadic modulation in the primate MTL may be analogous to hippocampal theta in rodents, which plays a role in collecting sensory information[272]. In addition to the two brain states proposed by Schroeder (continuous vs. rhythmic) and Corbetta (top-down vs. stimulus-driven), there also seem to be two prominent theta oscillations in the human hippocampus[377], [378]. The higher theta frequency seems to correspond to online predictive short-term sensory processing[379], like visual exploration (which is most prominent in the saccadic phase-reset response reported in our previous work), while the lower frequency theta oscillation is suggested to be a different brain state which is thought to be optimal for processing new stimuli[377]. We showed in our LFP work that higher latency image onset response has large slow-theta (or delta; 1-4Hz) evoked response in the MTL, which is consistent with the slow theta seen previously in humans and assumed to be involved in memory[216] (see [380]-for review). On the other hand, the lower latency saccade-onset response has been shown to be associated with a high-theta phase reset mechanism, which corresponds to how one explores one environment[195], [199]. This higher theta activity is akin to animal locomotive exploration, which involves theta oscillations to encode place and relevant stimuli[340], [367].

Therefore, the work provides context for how eye movements, theta and this CD signal can modulate MTL and hippocampal memory structures. Stimulation in line with this rhythm and the physiological signal is exciting, but work in this field has its limitations.

6.4 Primary Limitations

6.4.1 Stimulation Parameters

There are a wide variety of limitations in the stimulation parameters. By nature of using a Health Canada-approved clinical stimulator, we were limited to symmetric biphasic stimulation. Although cathodic asymmetrically balanced stimulation is typically considered more optimal for activation, this was not possible. Additionally, we were limited to one pair of electrodes in bipolar stimulation based on our current setup. In one study, memory effects were only found with simultaneous bilateral hippocampal stimulation. Network-based stimulation may be more effective with multi-site stimulation.

The intensities derived were different on a subject-by-subject basis. For standardization, it may have been preferable to determine stimulation parameters similar to previous studies rather than a new method for intensity and timing at the same time.

By the very nature of the size of electrodes, it was hard to determine which hippocampal subfield we were stimulating. This size is a limitation since a specific subfield could help support when stimulation would be effective since the hippocampus's circuitry is believed to be involved differently in memory formation. Recently, higher resolution MRI with auto segmentations is being accepted for determining location within hippocampal subfields.

Stimulation pulse width and frequency are also variables that could potentially be optimized. Theta burst stimulation is typically performed with lower frequencies than in this task, but we prioritized trying to place stimulation directly on peak or trough. However, less is understood about theta-burst at this 500Hz frequency.

6.4.2 Data Variability

There is variability in the data, as expected, based on typically small sample sizes in a clinical setting. Participants were of different ages, and the demographics are quite variable. Therefore, it is not easy to control factors such as age, gender, cognitive ability, and education.

Also, electrodes were placed based on the clinical need for seizure localization. By focusing on the MTL, which most patients have covered, we can use this appropriate study design to answer questions across different patients. Also, groups have started to collaborate and do cross-site studies to increase the numbers of iEEG data sets with specific tasks to better understand the brain's regions and how activity differs across a diverse population.

6.5 Future Directions

The original goal of this Ph.D. was to understand the relationship of the SPEAR model to human memory by studying the effects of stimulation timing on memory formation in individuals with epilepsy undergoing invasive electrical recordings. Although we did not improve memory, some major insights were obtained to enable some future exciting work to alleviate symptoms in neurological disorders.

Since eye movements seem to result in a CD, it is interesting to note that previous work links oculomotor CD impairments to various neurological diseases. In healthy individuals, it has been shown that the degree of psychosis was correlated with lack of eye-movement correction in a double saccade task, which results from inappropriate corollary discharges[381]. Investigations have also been conducted in individuals with Parkinson's disease where a CD in a saccade task was correlated with the integrity of their dopaminergic system. Patients with lower striatal dopamine suffered from the larger saccadic errors again in a double saccade task. This work suggested that perhaps the symptoms of Parkinson's Disease result partially from deficits in internal monitoring movements[382]. In the memory spectrum, in early-stage Alzheimer's, a different visual task has been investigated to determine the integrity of eye-movement-related CDs. Participants were asked to stare at perceived moving dots. While staring straight ahead or tracking eyes left or right, the participants would be asked in which direction, left or right, the dots seemed to be moving[383]. They did this in both fixation and smooth pursuit of a cross on the screen leftward or rightward. In fixation, both the elderly and Alzheimer's groups could perform and correctly identify the movement. However, with the eyes moving following a target, individuals with Alzheimer's, unlike healthy individuals, indicated the movement essentially followed the direction of their pursuit regardless of the optic flow, suggesting an issue with self-motion perception, which would likely result from anomalies in the eye-movement related CDs[383]. This study provided evidence that patients with Alzheimer's Disease suffer from deficits in eye-movement-related CDs. While we cannot assume or conclude that eye-movement-related CD deficits lead to dementia seen in patients with Alzheimer's Disease, the fact that these two phenomena occur together provides some credence to our hypothesis regarding the importance of the integrity of the CD circuitry for underlying memory function. In addition to known CD deficits, various studies have also shown that general eye movements and associated eye-movement patterns may be predictive of different stages of neurological diseases[384], [385].

There is an obvious connection between eye movement as a phase reset/CD and memory. It seems like a natural timing to investigate for stimulation. In our neuroprosthesis for memory chapter, we propose some considerations for requirements for a successful neuroprosthesis for

memory (Figure 6.1).

1. **Appropriate Anatomical Location:** An in depth understanding of the memory target or anatomical location.
2. **Appropriate Stimulation Parameters:** An optimal selection of stimulation parameters to modulate memory networks in a spatiotemporally precise manner.
3. **Appropriate Stimulation Contingency:** Closed-loop stimulation should be based on biomarkers that can be robustly extracted in a real-world environment and should not be dependent on a particular experimental paradigm.
4. **Appropriate Neural Interface Technology** High-density recording and stimulation capabilities, coupled with low power integrated circuits suitable for chronic implants.

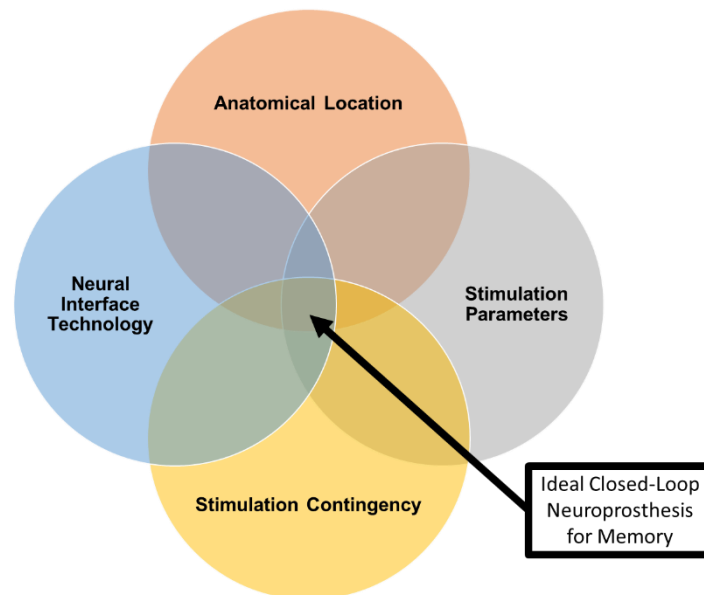


Figure 6.1| Closed Loop Stimulation Considerations: Different factors to consider for the development of an ideal closed-loop neuroprosthesis for memory. Also used in [64].

Therefore, I will draw on these requirements for some future steps given the contributions of this thesis:

Appropriate Anatomical Location

- Stimulation location was chosen as the hippocampus proper in grey matter contacts. Recently it has been shown that white matter stimulation proximal to the hippocampus may be most effective. Hence, stimulation location could be attempted in the white matter or afferent pathways to the hippocampus while still using the same theta-burst pattern on eye movements.
- Microstimulation could be optimized in specific hippocampal bodies through auto segmentation
- Bilateral stimulation of the hippocampus or network stimulation with multiple sites could also be considered.

Stimulation Parameters

- Pulse width, number of pulses per burst, and burst frequency can be further explored in the theta-burst protocol

Stimulation Contingency

- Behavioural effects have been shown to depend on the behavioural stage (encoding, maintenance or retrieval) in which stimulation was delivered. In this study, we only stimulated during encoding. A natural investigation would be to stimulate during the maintenance or retrieval stage.
- Since neural activity is modulated differently based on saccade direction, specific saccades may be stimulated while others could be left unstimulated. In fact, in the motor cortex, using transcranial magnetic stimulation, intermittent TBS has evoked different mechanisms than continuous TBS[386].

- A task could be created to specifically test the existence of the CD in the MTL and interrogate its function.

Neural Interface Technology

- Detection of the eye movement is currently implemented using an eye tracker. In a neural interface, ideally, the ongoing brain activity could be used to detect eye movement. Since an artifact exists in the iEEG due to eye movement[247], it is feasible to detect this movement using machine learning.
- Other hardware and implementation have not been discussed as the methodology was the purpose of this Ph.D. That being said, further research should also investigate the best implementation of such detection and stimulation on a chip.

7 Conclusion

As the global population ages, memory-related disorders are increasing, resulting in healthcare and economic burdens that will only continue to grow. Current treatment options are not effective. DBS has been considered a possible treatment for such memory disorders based on its success with other neurological conditions. Moving forward, DBS for memory will require a shift in research methodology. Most research has either used continuous open-loop stimulation (most of which have failed to show robust improvements in memory function) or closed-loop stimulation strategies that have not been tested outside of a well-controlled experimental environment. Finding more naturally occurring biomarkers of memory enables stimulation on naturally occurring events translated to the real world. Therefore, we identified the need to find this natural timing for stimulation and test such stimulation in a physiologically relevant manner.

The first contribution of this thesis was to identify that eye movement in response to a visual stimulus is a more appropriate timing cue than image presentation. Eye movements induce a theta phase reset with a peak and trough. This peak and trough could be used for subsequent stimulation in MTL structures or other structures in the memory network.

The second contribution was a further investigation into the mechanism behind this saccadic response in the MTL structures. Specifically, single units were used to identify the cellular mechanisms during the perisaccadic interval. There was predominantly inhibition which is in line with both a phase reset and corollary discharge. By providing evidence through single units, we can suggest that such a response is an internally generated movement not previously probed in mnemonic structures. It is easy to understand the CD to stabilize vision or compare our internal and external surroundings, but what this CD may signify in the MTL memory structures is not so clear. Such circuits can also be involved in higher-order activities in gating our senses and how we interact, contextualize and remember the world around us. Such an idea was postulated as early as 1978, where it was hypothesized that a CD might act as a mechanism of control and integration in thinking itself[387]. Alternatively, the hippocampus is very much engaged in relational binding in time, space and such a preparatory signal may be necessary to align information accordingly to its relevant contextual relationship[388]. This finding will provide future work for interrogating the

CD circuit in animal studies through optogenetic and other manipulations. Additionally, we can better understand how such a CD functions in the MTL and what happens when it dysfunctions.

Finally, the thesis brought these two contributions together to investigate contingent stimulation on the saccadic ERP. By demonstrating that we could modify memory through such stimulation, it provides potential avenues for future research with these parameters. TBS contingent on saccadic ERP presents a natural stimulation timing that can be translated to the real world, with possible adaptation to stimulation parameters, location, or behavioural stage.

Our work in saccadic ERP contingent stimulation provides insight into DBS for memory. Specifically, it provides a novel way to utilize eye movements as windows into brain functionality and modulate based on the phases biased for encoding and retrieval, respectively. This work can lead to further understanding of mechanisms of memory formation and DBS as a treatment.

References

- [1] “2020 Alzheimer’s disease facts and figures,” *Alzheimer’s Dement.*, vol. 16, no. 3, pp. 391–460, 2020, doi: 10.1002/alz.12068.
- [2] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. Arlington, 2013.
- [3] L. E. Hebert, J. Weuve, P. A. Scherr, and D. A. Evans, “Alzheimer disease in the United States (2010-2050) estimated using the 2010 census,” *Neurology*, vol. 80, no. 19, pp. 1778–1783, May 2013, doi: 10.1212/WNL.0b013e31828726f5.
- [4] L. W. Chambers, C. Bancej, and I. McDowell, “Prevalence and Monetary Costs of Dementia in Canada,” *Alzheimers Soc. Canada*, no. May 2015, p. 70, 2016, doi: 10.1017/CBO9781107415324.004.
- [5] A. Wimo *et al.*, “The worldwide costs of dementia 2015 and comparisons with 2010,” *Alzheimer’s Dement.*, vol. 13, no. 1, pp. 1–7, Jan. 2017, doi: 10.1016/j.jalz.2016.07.150.
- [6] S. Heschem, L. W. Lim, A. Jahanshahi, A. Blokland, and Y. Temel, “Deep brain stimulation in dementia-related disorders,” *Neurosci. Biobehav. Rev.*, vol. 37, no. 10, pp. 2666–2675, 2013, doi: 10.1016/j.neubiorev.2013.09.002.
- [7] T. Sankar, N. Lipsman, and A. M. Lozano, “Deep Brain Stimulation for Disorders of Memory and Cognition,” *Neurotherapeutics*, vol. 11, no. 3, pp. 527–534, Apr. 2014, doi: 10.1007/s13311-014-0275-0.
- [8] A. M. Lozano and N. Lipsman, “Probing and regulating dysfunctional circuits using deep brain stimulation,” *Neuron*, vol. 77, no. 3, pp. 406–24, Feb. 2013, doi: 10.1016/j.neuron.2013.01.020.
- [9] A. L. Benabid, P. Pollak, A. Louveau, S. Henry, and J. De Rougemont, “Combined (thalamotomy and stimulation) stereotactic surgery of the vim thalamic nucleus for bilateral parkinson disease,” *Stereotact. Funct. Neurosurg.*, 1987, doi: 10.1159/000100803.

- [10] P. E. Holtzheimer *et al.*, “Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression,” *Arch. Gen. Psychiatry*, vol. 69, no. 2, pp. 150–158, Feb. 2012, doi: 10.1001/archgenpsychiatry.2011.1456.
- [11] R. G. HEATH, R. R. MONROE, and W. A. MICKLE, “Stimulation of the amygdaloid nucleus in a schizophrenic patient.,” *Am. J. Psychiatry*, 1955, doi: 10.1176/ajp.111.11.862.
- [12] N. Suthana *et al.*, “Memory Enhancement and Deep-Brain Stimulation of the Entorhinal Area,” *N. Engl. J. Med.*, vol. 366, no. 6, pp. 502–510, Feb. 2012, doi: 10.1056/NEJMoa1107212.
- [13] J. Fell *et al.*, “Memory modulation by weak synchronous deep brain stimulation: a pilot study.,” *Brain Stimul.*, vol. 6, no. 3, pp. 270–3, May 2013, doi: 10.1016/j.brs.2012.08.001.
- [14] J. P. Miller, J. A. Sweet, C. M. Bailey, C. N. Munyon, H. O. Luders, and P. S. Fastenau, “Visual-spatial memory may be enhanced with theta burst deep brain stimulation of the fornix: A preliminary investigation with four cases,” *Brain*, vol. 138, no. 7, pp. 1833–1842, Jul. 2015, doi: 10.1093/brain/awv095.
- [15] A. W. Laxton *et al.*, “A phase I trial of deep brain stimulation of memory circuits in Alzheimer’s disease,” *Ann. Neurol.*, vol. 68, no. 4, pp. 521–534, 2010, doi: 10.1002/ana.22089.
- [16] T. W. Berger, R. E. Hampson, D. Song, A. Goonawardena, V. Z. Marmarelis, and S. A. Deadwyler, “A cortical neural prosthesis for restoring and enhancing memory.,” *J. Neural Eng.*, vol. 8, no. 4, p. 046017, Aug. 2011, doi: 10.1088/1741-2560/8/4/046017.
- [17] D. U. Jeong, J. E. Lee, S. E. Lee, W. S. Chang, S. J. Kim, and J. W. Chang, “Improvements in memory after medial septum stimulation are associated with changes in hippocampal cholinergic activity and neurogenesis,” *Biomed Res. Int.*, vol. 2014, p. 568587, 2014, doi: 10.1155/2014/568587.
- [18] S. A. Deadwyler *et al.*, “A cognitive prosthesis for memory facilitation by closed-loop

- functional ensemble stimulation of hippocampal neurons in primate brain,” *Exp. Neurol.*, vol. 287, pp. 452–460, 2016, doi: 10.1016/j.expneurol.2016.05.031.
- [19] S. S. D. Stone *et al.*, “Stimulation of Entorhinal Cortex Promotes Adult Neurogenesis and Facilitates Spatial Memory,” *J. Neurosci.*, vol. 31, no. 38, pp. 13469–13484, 2011, doi: 10.1523/JNEUROSCI.3100-11.2011.
- [20] X. Liu *et al.*, “Optogenetic stimulation of a hippocampal engram activates fear memory recall.,” *Nature*, vol. 484, no. 7394, pp. 381–5, Apr. 2012, doi: 10.1038/nature11028.
- [21] D. J. Lee *et al.*, “Septohippocampal Neuromodulation Improves Cognition after Traumatic Brain Injury,” *J. Neurotrauma*, vol. 11, no. 22, p. 150902125930001, Nov. 2015, doi: 10.1089/neu.2014.3744.
- [22] W. B. Scoville and B. Milner, “Loss of recent memory after bilateral hippocampal lesions. 1957.,” *J. Neuropsychiatry Clin. Neurosci.*, vol. 20, no. 11, pp. 11–21, Feb. 1957, doi: 10.1136/jnnp.20.1.11.
- [23] G. Fernandez, A. Hufnagel, C. Helmstaedter, J. Zentner, and C. E. Elger, “Memory function during low intensity hippocampal electrical stimulation in patients with temporal lobe epilepsy,” *Eur. J. Neurol.*, vol. 3, no. December, pp. 335–344, 1996.
- [24] M. E. Lacruz, A. Valentín, J. J. G. Seoane, R. G. Morris, R. P. Selway, and G. Alarcón, “Single pulse electrical stimulation of the hippocampus is sufficient to impair human episodic memory.,” *Neuroscience*, vol. 170, no. 2, pp. 623–32, Oct. 2010, doi: 10.1016/j.neuroscience.2010.06.042.
- [25] J. Jacobs *et al.*, “Direct Electrical Stimulation of the Human Entorhinal Region and Hippocampus Impairs Memory,” *Neuron*, vol. 92, no. 5, pp. 983–990, Dec. 2016, doi: 10.1016/j.neuron.2016.10.062.
- [26] S. Jun, J. S. Kim, and C. K. Chung, “Direct Stimulation of Human Hippocampus During Verbal Associative Encoding Enhances Subsequent Memory Recollection,” *Front. Hum. Neurosci.*, vol. 13, no. February, pp. 1–10, 2019, doi: 10.3389/fnhum.2019.00023.

- [27] E. Halgren, C. L. Wilson, and J. M. Stapleton, “Human medial temporal-lobe stimulation disrupts both formation and retrieval of recent memories,” *Brain Cogn.*, vol. 4, no. 3, pp. 287–295, 1985, doi: 10.1016/0278-2626(85)90022-3.
- [28] E. Halgren and C. L. Wilson, “Recall deficits produced by afterdischarges in the human hippocampal formation and amygdala,” *Electroencephalogr. Clin. Neurophysiol.*, vol. 61, no. 5, pp. 375–380, 1985, doi: 10.1016/0013-4694(85)91028-4.
- [29] S. G. Coleshill *et al.*, “Material-Specific Recognition Memory Deficits Elicited by Unilateral Hippocampal Electrical Stimulation,” *J. Neurosci.*, vol. 24, no. 7, 2004.
- [30] M. B. Merkow, J. F. Burke, A. G. Ramayya, A. D. Sharan, M. R. Sperling, and M. J. Kahana, “Stimulation of the human medial temporal lobe between learning and recall selectively enhances forgetting,” *Brain Stimul.*, pp. 1–6, 2016, doi: 10.1016/j.brs.2016.12.011.
- [31] D. J. Lee and A. M. Lozano, “Current Status of Deep Brain Stimulation for Alzheimer’s Disease: From Chance Observation to Clinical Trials,” *Cold Spring Harb. Symp. Quant. Biol.*, vol. LXXXIII, p. 037440, 2019, doi: 10.1101/sqb.2018.83.037440.
- [32] UN, “World Population Ageing 2020 Highlights,” *Population Division of the United Nations Department of Economic and Social Affairs*, 2020.
https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/files/documents/2020/Sep/un_pop_2020_pf_ageing_10_key_messages.pdf (accessed Apr. 05, 2021).
- [33] Statistics Canada, “Demographic estimates by age and sex, provinces and territories,” *Statistics Canada*, 2020. <https://www150.statcan.gc.ca/n1/pub/71-607-x/71-607-x2020018-eng.htm> (accessed Apr. 06, 2021).
- [34] WHO, “Dementia- Key Facts,” 2020. <https://www.who.int/news-room/fact-sheets/detail/dementia> (accessed Apr. 06, 2021).
- [35] Mental Health Commission of Canada, “Making the Case for Investing in Mental Health in

Canada,” *Ment. Heal. Commison Canada*, pp. 1–27, 2011, [Online]. Available: http://www.mentalhealthcommission.ca/English/system/files/private/document/Investing_in_Mental_Health_FINAL_Version_ENG.pdf.

- [36] Alzheimer Society of Canada, “Rising Tide : The Impact of Dementia on Canadian Society. Executive Summary.,” *Dementia*, pp. 1–24, 2010.
- [37] I. McDowell *et al.*, “Canadian Study of Health and Aging: Study methods and prevalence of dementia,” *CMAJ*, vol. 150, no. 6, pp. 899–912, 1994, Accessed: Apr. 03, 2021. [Online]. Available: </pmc/articles/PMC1486712/?report=abstract>.
- [38] T. C. I. of H. R. Neurological Health Charities Canada, The Public Health Agency of Canada, Health Canada, *Mapping Connections an Understanding of Neurological Conditions- THE NATIONAL POPULATION HEALTH STUDY OF NEUROLOGICAL CONDITIONS*. 2014.
- [39] S. Alladi *et al.*, “Focal cortical presentations of Alzheimer’s disease,” *Brain*, vol. 130, no. 10, pp. 2636–2645, 2007, doi: 10.1093/brain/awm213.
- [40] G. D. Rabinovici *et al.*, “A β amyloid and glucose metabolism in three variants of primary progressive aphasia,” *Ann. Neurol.*, vol. 64, no. 4, pp. 388–401, Oct. 2008, doi: 10.1002/ana.21451.
- [41] M. M. Swanberg, R. E. Tractenberg, R. Mohs, L. J. Thal, and J. L. Cummings, “Executive dysfunction in Alzheimer disease,” *Arch. Neurol.*, vol. 61, no. 4, pp. 556–560, Apr. 2004, doi: 10.1001/archneur.61.4.556.
- [42] S. Chi, J. T. Yu, M. S. Tan, and L. Tan, “Depression in Alzheimer’s disease: Epidemiology, mechanisms, and management,” *J. Alzheimer’s Dis.*, vol. 42, no. 3, pp. 739–755, 2014, doi: 10.3233/JAD-140324.
- [43] L. Ferretti, S. M. Mccurry, L. Gibbons, and L. Teri, “Anxiety and Alzheimer ’ s Disease,” *J. Geriatr. Psychiatry Neurol.*, vol. 14, no. 1, pp. 52–58, 2001.
- [44] G. M. McKhann *et al.*, “The diagnosis of dementia due to Alzheimer’s disease:

Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease," *Alzheimer's Dement.*, vol. 7, no. 3, pp. 263–269, 2011, doi: 10.1016/j.jalz.2011.03.005.

- [45] I. G. McKeith *et al.*, "Diagnosis and management of dementia with Lewy bodies," *Neurology*, vol. 89, no. 1. Lippincott Williams and Wilkins, pp. 88–100, Jul. 04, 2017, doi: 10.1212/WNL.0000000000004058.
- [46] M. L. Gorno-Tempini *et al.*, "Classification of primary progressive aphasia and its variants," *Neurology*, vol. 76, no. 11, pp. 1–10, Mar. 2011, doi: 10.1212/WNL.0b013e31821103e6.
- [47] K. Rascovsky *et al.*, "Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia," *Brain*, vol. 134, no. 9, pp. 2456–2477, 2011, doi: 10.1093/brain/awr179.
- [48] S. E. Lee *et al.*, "Clinicopathological correlations in corticobasal degeneration," *Annals of Neurology*, vol. 70, no. 2. pp. 327–340, Aug. 2011, doi: 10.1002/ana.22424.
- [49] M. C. Tartaglia *et al.*, "Chronic traumatic encephalopathy and other neurodegenerative proteinopathies," *Front. Hum. Neurosci.*, vol. 8, no. JAN, p. 30, Jan. 2014, doi: 10.3389/fnhum.2014.00030.
- [50] K. G. Yiannopoulou and S. G. Papageorgiou, "Current and future treatments for Alzheimer's disease," *Therapeutic Advances in Neurological Disorders*, vol. 6, no. 1. SAGE Publications, pp. 19–33, 2013, doi: 10.1177/1756285612461679.
- [51] L. Blanco-Silvente *et al.*, "Discontinuation, Efficacy, and Safety of Cholinesterase Inhibitors for Alzheimer's Disease: A Meta-Analysis and Meta-Regression of 43 Randomized Clinical Trials Enrolling 16 106 Patients," *Int. J. Neuropsychopharmacol.*, vol. 20, no. 7, pp. 519–528, 2017, doi: 10.1093/ijnp/pyx012.
- [52] C. Ballard and A. Corbett, "Management of neuropsychiatric symptoms in people with dementia," *CNS Drugs*, vol. 24, no. 9. CNS Drugs, pp. 729–739, 2010, doi:

10.2165/11319240-000000000-00000.

- [53] G. S. Watson and J. B. Leverenz, “Profile of cognitive impairment in Parkinson’s disease,” *Brain Pathol.*, vol. 20, no. 3, pp. 640–5, May 2010, doi: 10.1111/j.1750-3639.2010.00373.x.
- [54] M. A. Hely, W. G. J. Reid, M. A. Adena, G. M. Halliday, and J. G. L. Morris, “The Sydney Multicenter Study of Parkinson’s disease: The inevitability of dementia at 20 years,” *Mov. Disord.*, vol. 23, no. 6, pp. 837–844, Apr. 2008, doi: 10.1002/mds.21956.
- [55] S. L. Kowal, T. M. Dall, R. Chakrabarti, M. V. Storm, and A. Jain, “The current and projected economic burden of Parkinson’s disease in the United States,” *Mov. Disord.*, vol. 28, no. 3, pp. 311–318, Mar. 2013, doi: 10.1002/mds.25292.
- [56] H. Braak, K. Del Tredici, U. Rüb, R. A. I. De Vos, E. N. H. Jansen Steur, and E. Braak, “Staging of brain pathology related to sporadic Parkinson’s disease,” *Neurobiol. Aging*, vol. 24, no. 2, pp. 197–211, 2003, doi: 10.1016/S0197-4580(02)00065-9.
- [57] H. Braak and E. Braak, “Neuropathological staging of Alzheimer-related changes,” *Acta Neuropathol.*, vol. 82, pp. 239–259, 1991, doi: 10.1109/ICINIS.2015.10.
- [58] Epilepsy Canada, “Epilepsy Facts - Epilepsy Canada.” <http://www.epilepsy.ca/epilepsy-facts.html> (accessed Oct. 25, 2015).
- [59] “WHO | Epilepsy,” *WHO*, 2017. <http://www.who.int/mediacentre/factsheets/fs999/en/> (accessed Dec. 09, 2017).
- [60] B. Hermann and M. Seidenberg, “Epilepsy and cognition,” *Epilepsy Curr.*, vol. 7, no. 1, pp. 1–6, 2007, doi: 10.1111/j.1535-7511.2007.00151.x.
- [61] C. E. Elger, C. Helmstaedter, and M. Kurthen, “Chronic epilepsy and cognition,” *Lancet Neurol.*, vol. 3, no. November, pp. 663–672, 2004, doi: 10.1016/S1474-4422(04)00906-8.
- [62] L. R. Squire and J. T. Wixted, “The cognitive neuroscience of human memory since H.M.,” *Annu. Rev. Neurosci.*, vol. 34, pp. 259–288, 2011, doi: 10.1146/annurev-neuro-

061010-113720.

- [63] L. R. Squire, “Memory systems of the brain: A brief history and current perspective,” *Neurobiol. Learn. Mem.*, vol. 82, no. 3, pp. 171–177, 2004, doi: 10.1016/j.nlm.2004.06.005.
- [64] K. Patel *, C. Katz *, K. D. Duncan, and T. A. Valiante, “Neuroprosthesis for Memory Chapter: Springer Handbook of Neural Engineering (In Press),” in *Handbook of Neuroengineering*, Springer, 2021.
- [65] E. Tulving, “Episodic and Semantic Memory,” in *Organization of memory*, 1972, pp. 381–403.
- [66] E. Tulving, “EPISODIC MEMORY: From Mind to Brain,” *Annu. Rev. Psychol.*, vol. 53, pp. 1–25, 2002, doi: 0084-6570/02/0201-0001.
- [67] E. Tulving, “Ebbinghaus’s Memory. What Did He Learn and Remember?,” *J. Exp. Psychol. Learn. Mem. Cogn.*, 1985, doi: 10.1037/0278-7393.11.3.485.
- [68] H. Eichenbaum, “Hippocampus: Cognitive processes and neural representations that underlie declarative memory,” *Neuron*, vol. 44, no. 1, pp. 109–120, 2004, doi: 10.1016/j.neuron.2004.08.028.
- [69] N. L. M. Cappaert, N. M. Van Strien, and M. P. Witter, *Hippocampal Formation*, Fourth Edi. New York: Elsevier Inc., 2014.
- [70] B. L. McNaughton, J. L. McClelland, and R. C. O. Reilly, “Why There Are Complementary Learning Systems in the Hippocampus and Neocortex: Insights From the Successes and Failures of Connectionist Models of Learning and Memory,” *Psychol. Rev.*, vol. 102, no. 3, pp. 419–457, 1995, doi: 10.1037/0033-295X.102.3.419.
- [71] J. K. Leutgeb, S. Leutgeb, M.-B. Moser, and E. I. Moser, “Pattern Separation in the Dentate Gyrus and CA3 of the Hippocampus.” Accessed: Apr. 07, 2021. [Online]. Available: <http://science.sciencemag.org/>.

- [72] A. Treves and E. T. Rolls, “Computational Analysis of the role of hippocampus in memory,” vol. 4, no. 3, pp. 374–391, 1994.
- [73] D. Kumaran and E. A. Maguire, “Match Mismatch Processes Underlie Human Hippocampal Responses to Associative Novelty,” *J. Neurosci.*, vol. 27, no. 32, pp. 8517–8524, 2007, doi: 10.1523/JNEUROSCI.1677-07.2007.
- [74] K. Duncan, N. Ketz, S. J. Inati, and L. Davachi, “Evidence for area CA1 as a match/mismatch detector: A high-resolution fMRI study of the human hippocampus,” *Hippocampus*, vol. 22, no. 3, pp. 389–398, 2012, doi: 10.1002/hipo.20933.
- [75] J. Chen, R. K. Olsen, A. R. Preston, G. H. Glover, and A. D. Wagner, “Associative retrieval processes in the human medial temporal lobe: hippocampal retrieval success and CA1 mismatch detection.,” *Learn. Mem.*, vol. 18, no. 8, pp. 523–528, 2011, doi: 10.1101/lm.2135211.
- [76] M. E. Hasselmo, “The Role of Hippocampal Regions CA3 and CA1 in Matching Entorhinal Input With Retrieval of Associations Between Objects and Context: Theoretical Comment on Lee et al. (2005).,” *Behav. Neurosci.*, vol. 119, no. 1, pp. 342–345, 2005, doi: 10.1037/0735-7044.119.1.342.
- [77] L. R. Squire and P. Alvarez, “Retrograde amnesia and memory consolidation: a neurobiological perspective,” *Curr. Opin. Neurobiol.*, vol. 5, no. 2, pp. 169–177, Apr. 1995, doi: 10.1016/0959-4388(95)80023-9.
- [78] L. R. Squire, “Memory and the Hippocampus: A Synthesis From Findings With Rats, Monkeys, and Humans,” *Psychol. Rev.*, vol. 99, no. 2, pp. 195–231, 1992, doi: 10.1037/0033-295X.99.2.195.
- [79] L. Nadel and M. Moscovitch, “Memory consolidation, retrograde amnesia and the hippocampal complex,” *Curr. Opin. Neurobiol.*, vol. 7, pp. 217–227, 1997.
- [80] T. Kitamura, S. K. Ogawa, D. S. Roy, and T. Okuyama, “Engrams and circuits crucial for systems consolidation of a memory,” vol. 78, no. April, pp. 73–78, 2017, doi:

10.1126/science.aam6808.

- [81] S. A. Josselyn, S. Köhler, and P. W. Frankland, “Heroes of the engram,” *J. Neurosci.*, vol. 37, no. 18, pp. 4647–4657, May 2017, doi: 10.1523/JNEUROSCI.0056-17.2017.
- [82] D. O. Hebb, “The organization of behavior: A Neuropsychological Approach,” *The American Journal of Psychology*, vol. 63, no. 4, p. 633, 1949, doi: 10.2307/1418888.
- [83] S. J. Martin, P. D. Grimwood, and R. G. M. Morris, “Synaptic plasticity and memory: An Evaluation of the Hypothesis,” *Annu. Rev. Neurosci.*, no. Hebb 1949, pp. 649–711, 2000, doi: 10.1146/annurev.neuro.23.1.649.
- [84] K. S. Giovanello, M. Verfaellie, and M. M. Keane, “Disproportionate deficit in associative recognition relative to item recognition in global amnesia,” *Cogn. Affect. Behav. Neurosci.*, vol. 3, no. 3, pp. 186–194, Sep. 2003, doi: 10.3758/CABN.3.3.186.
- [85] A. R. Mayes *et al.*, “Associative recognition in a patient with selective hippocampal lesions and relatively normal item recognition,” *Hippocampus*, vol. 14, no. 6, pp. 763–784, Jan. 2004, doi: 10.1002/hipo.10211.
- [86] N. a Suthana, A. D. Ekstrom, S. Moshirvaziri, B. Knowlton, and S. Y. Bookheimer, “Human Hippocampal CA1 Involvement during Allocentric Encoding of Spatial Information,” *J. Neurosci.*, vol. 29, no. 34, pp. 10512–10519, Aug. 2009, doi: 10.1523/JNEUROSCI.0621-09.2009.
- [87] P. K. Pilly and S. Grossberg, “How Do Spatial Learning and Memory Occur in the Brain ? Coordinated Learning of Entorhinal Grid Cells and Hippocampal Place Cells,” *J. Cogn. Neurosci.*, pp. 1031–1054, 2012.
- [88] N. Burgess, E. A. Maguire, and J. O’Keefe, “The Human Hippocampus and Spatial and Episodic Memory,” *Neuron*, vol. 35, no. 4, pp. 625–641, Aug. 2002, doi: 10.1016/S0896-6273(02)00830-9.
- [89] N. B. Turk-Browne, “The hippocampus as a visual area organized by space and time: A spatiotemporal similarity hypothesis,” *Vision Res.*, vol. 165, no. May 2018, pp. 123–130,

2019, doi: 10.1016/j.visres.2019.10.007.

- [90] György Buzsáki and D. Tingley, “Space and time: The hippocampus as a sequence generator György,” *Trends Cogn. Sci.*, vol. 22, no. 10, pp. 853–869, 2018, doi: 10.1016/j.tics.2018.07.006.Space.
- [91] G. Umbach *et al.*, “Time cells in the human hippocampus and entorhinal cortex support episodic memory,” *Proc. Natl. Acad. Sci.*, p. 202013250, 2020, doi: 10.1073/pnas.2013250117.
- [92] M. Tsitsiklis *et al.*, “Single-Neuron Representations of Spatial Targets in Humans,” *Curr. Biol.*, vol. 30, no. 2, pp. 245-253.e4, 2020, doi: 10.1016/j.cub.2019.11.048.
- [93] J. Jacobs *et al.*, “Direct recordings of grid-like neuronal activity in human spatial navigation,” *Nat. Neurosci.*, no. August, pp. 8–11, 2013, doi: 10.1038/nn.3466.
- [94] S. A. Small, S. A. Schobel, R. B. Buxton, M. P. Witter, and C. A. Barnes, “A pathophysiological framework of hippocampal dysfunction in ageing and disease,” *Nature Reviews Neuroscience*, vol. 12, no. 10. NIH Public Access, pp. 585–601, Oct. 2011, doi: 10.1038/nrn3085.
- [95] A. M. Lozano *et al.*, “Deep brain stimulation: current challenges and future directions,” *Nature Reviews Neurology*, vol. 15, no. 3. Nature Publishing Group, pp. 148–160, Mar. 01, 2019, doi: 10.1038/s41582-018-0128-2.
- [96] J. O. Dostrovsky and A. M. Lozano, “Mechanisms of deep brain stimulation,” *Mov. Disord.*, vol. 17, no. S3, pp. S63–S68, 2002, doi: 10.1002/mds.10143.
- [97] A. W. Laxton, N. Lipsman, and A. M. Lozano, *Deep brain stimulation for cognitive disorders*, 1st ed., vol. 116, no. 1985. Elsevier B.V., 2013.
- [98] L. Frank, *The Pleasure Shock: The Rise of Deep Brain Stimulation and Its Forgotten Inventor*. Dutton, 2018.
- [99] C. Universitaria, “Deep-Brain Stimulation of the Subthalamic Nucleus or the Pars Interna

of the Globus Pallidus in Parkinson's Disease," *N. Engl. J. Med.*, vol. 345, no. 13, pp. 956–963, 2002, doi: 10.1056/nejmoa000827.

- [100] C. Hamani *et al.*, "Memory enhancement induced by hypothalamic/fornix deep brain stimulation," *Ann. Neurol.*, vol. 63, no. 1, pp. 119–123, 2008, doi: 10.1002/ana.21295.
- [101] J. P. Aggleton, S. M. O'Mara, S. D. Vann, N. F. Wright, M. Tsanov, and J. T. Erichsen, "Hippocampal-anterior thalamic pathways for memory: Uncovering a network of direct and indirect actions," *European Journal of Neuroscience*, vol. 31, no. 12, pp. 2292–2307, 2010, doi: 10.1111/j.1460-9568.2010.07251.x.
- [102] J. W. Papez, "A Proposed Mechanism of Emotion," *Arch. Neurol. Psychiatry*, vol. 38, no. 4, pp. 725–743, 1937.
- [103] T. Sankar *et al.*, "Deep brain stimulation influences brain structure in Alzheimer's disease," *Brain Stimul.*, vol. 8, no. 3, pp. 645–654, May 2015, doi: 10.1016/j.brs.2014.11.020.
- [104] H.-J. Freund *et al.*, "Cognitive functions in a patient with parkinson-dementia syndrome undergoing deep-brain stimulation," *Arch.Neurol.*, vol. 66, no. 6, pp. 781–785, 2009.
- [105] J. Kuhn *et al.*, "Deep brain stimulation of the nucleus basalis of Meynert in Alzheimer's dementia," *Mol. Psychiatry*, vol. 20, no. 3, pp. 353–360, 2015, doi: 10.1038/mp.2014.32.
- [106] J. Kuhn *et al.*, "Deep Brain Stimulation of the Nucleus Basalis of Meynert in Early Stage of Alzheimer's Dementia," *Brain Stimul.*, vol. 8, no. 4, pp. 838–839, 2015, doi: 10.1016/j.brs.2015.04.002.
- [107] Y.-S. Oh, H. J. Kim, K. J. Lee, Y. I. Kim, S.-C. Lim, and Y.-M. Shon, "Cognitive improvement after long-term electrical stimulation of bilateral anterior thalamic nucleus in refractory epilepsy patients.," *Seizure*, vol. 21, no. 3, pp. 183–7, Apr. 2012, doi: 10.1016/j.seizure.2011.12.003.
- [108] A. L. Velasco, F. Velasco, M. Velasco, D. Trejo, G. Castro, and J. D. Carrillo-Ruiz, "Electrical stimulation of the hippocampal epileptic foci for seizure control: A double-

- blind, long-term follow-up study,” *Epilepsia*, vol. 48, no. 10, pp. 1895–1903, 2007, doi: 10.1111/j.1528-1167.2007.01181.x.
- [109] R. S. McLachlan, S. Pigott, J. F. Tellez-Zenteno, S. Wiebe, and A. Parrent, “Bilateral hippocampal stimulation for intractable temporal lobe epilepsy: Impact on seizures and memory,” *Epilepsia*, vol. 51, no. 2, pp. 304–307, 2010, doi: 10.1111/j.1528-1167.2009.02332.x.
- [110] C. Boëx *et al.*, “Chronic deep brain stimulation in mesial temporal lobe epilepsy.,” *Seizure*, vol. 20, no. 6, pp. 485–90, Jul. 2011, doi: 10.1016/j.seizure.2011.03.001.
- [111] M. Miatton *et al.*, “The cognitive effects of amygdalohippocampal deep brain stimulation in patients with temporal lobe epilepsy,” *Epilepsy Behav.*, vol. 22, no. 4, pp. 759–764, 2011, doi: 10.1016/j.yebeh.2011.09.016.
- [112] A. M. Lozano *et al.*, “A Phase II Study of Fornix Deep Brain Stimulation in Mild Alzheimer’s Disease,” *J. Alzheimer’s Dis.*, vol. 54, no. 2, pp. 777–787, 2016, doi: 10.3233/JAD-160017.
- [113] J. S. Leoutsakos *et al.*, “Deep Brain Stimulation Targeting the Fornix for Mild Alzheimer Dementia (the ADvance Trial): A Two Year Follow-up including results of delayed activation,” *J. Alzheimer’s Dis.*, vol. 64, no. 2, pp. 597–606, 2018, doi: 10.3233/JAD-180121.Deep.
- [114] R. C. Knowlton *et al.*, “Magnetic source imaging versus intracranial electroencephalogram in epilepsy surgery: A prospective study,” *Ann. Neurol.*, vol. 59, no. 5, pp. 835–842, 2006, doi: 10.1002/ana.20857.
- [115] F. Semah *et al.*, “Is the underlying cause of epilepsy a major prognostic factor for recurrence?,” *Neurology*, vol. 51, no. 5, pp. 1256–1262, 1998, doi: 10.1212/WNL.51.5.1256.
- [116] M. T. Kucewicz *et al.*, “Electrical Stimulation Modulates High γ Activity and Human Memory Performance,” vol. 5, no. February, pp. 1–14, 2018.

- [117] M. T. Kucewicz *et al.*, “Evidence for verbal memory enhancement with electrical brain stimulation in the lateral temporal cortex,” *Brain*, vol. 141, no. 4, pp. 971–978, 2018, doi: 10.1093/brain/awx373.
- [118] E. A. Mankin *et al.*, “Stimulation of the right entorhinal white matter enhances visual memory encoding in humans,” *Brain Stimul.*, vol. 14, no. 1, pp. 131–140, 2021, doi: 10.1016/j.brs.2020.11.015.
- [119] U. R. Mohan *et al.*, “The effects of direct brain stimulation in humans depend on frequency, amplitude, and white-matter proximity,” *Brain Stimul.*, vol. 13, no. 5, pp. 1183–1195, 2020, doi: 10.1016/j.brs.2020.05.009.
- [120] J. Larson, D. Wong, G. Lynch, and Larson, “Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation,” *Brain Res.*, vol. 368, no. 2, pp. 347–350, Mar. 1986.
- [121] J. M. Hyman, B. P. Wyble, V. Goyal, C. A. Rossi, and M. E. Hasselmo, “Stimulation in hippocampal region CA1 in behaving rats yields long-term potentiation when delivered to the peak of theta and long-term depression when delivered to the trough,” *J. Neurosci.*, vol. 23, no. 37, pp. 11725–31, Dec. 2003, Accessed: Nov. 23, 2015. [Online]. Available: <http://www.jneurosci.org/content/23/37/11725.abstract>.
- [122] C. Hölscher, R. Anwyl, and M. J. Rowan, “Stimulation on the positive phase of hippocampal theta rhythm induces long-term potentiation that can be depotentiated by stimulation on the negative phase in area CA1 in vivo,” *J. Neurosci.*, vol. 17, no. 16, pp. 6470–6477, 1997.
- [123] P. T. Huerta and J. E. Lisman, “Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro,” *Neuron*, vol. 15, no. 5, pp. 1053–1063, Nov. 1995, doi: 10.1016/0896-6273(95)90094-2.
- [124] J. Kwag and O. Paulsen, “The timing of external input controls the sign of plasticity at local synapses,” *Nat. Neurosci.*, vol. 12, no. 10, pp. 1219–21, 2009, doi: 10.1038/nn.2388.

- [125] A. S. Titiz *et al.*, “Theta-burst microstimulation in the human entorhinal area improves memory specificity,” *Elife*, vol. 6, p. e29515, Oct. 2017, doi: 10.7554/eLife.29515.
- [126] C. S. Inman *et al.*, “Direct electrical stimulation of the amygdala enhances declarative memory in humans,” *Proc. Natl. Acad. Sci.*, vol. 115, no. 1, pp. 98–103, 2018, doi: 10.1073/pnas.1714058114.
- [127] E. Solomon *et al.*, “Theta-burst stimulation entrains frequency-specific oscillatory responses,” *Res. Sq.*, pp. 1–28, 2021.
- [128] Y. Ezzyat *et al.*, “Direct Brain Stimulation Modulates Encoding States and Memory Performance in Humans,” *Curr. Biol.*, vol. 27, no. 9, pp. 1251–1258, May 2017, doi: 10.1016/j.cub.2017.03.028.
- [129] N. Hansen *et al.*, “Memory encoding-related anterior hippocampal potentials are modulated by deep brain stimulation of the entorhinal area,” *Hippocampus*, vol. 28, no. 1, pp. 12–17, 2018, doi: 10.1002/hipo.22808.
- [130] K. Kim, A. Schedlbauer, M. Rollo, S. Karunakaran, A. D. Ekstrom, and N. Tandon, “Network-based brain stimulation selectively impairs spatial retrieval,” *Brain Stimul.*, vol. 11, no. 1, pp. 213–221, 2018, doi: 10.1016/j.brs.2017.09.016.
- [131] V. S. Natu, J. J. Lin, A. Burks, A. Arora, M. D. Rugg, and B. Lega, “Stimulation of the posterior cingulate impairs episodic memory encoding,” *J. Neurosci.*, vol. 39, no. 36, pp. 7173–7182, 2019, doi: 10.1101/497818.
- [132] S. K. Bick *et al.*, “Caudate stimulation enhances learning,” *Brain*, vol. 142, no. 10, pp. 2930–2937, 2019, doi: 10.1093/brain/awz254.
- [133] S. Alagapan, C. Lustenberger, E. Hadar, H. W. Shin, and F. Fröhlich, “Low-frequency direct cortical stimulation of left superior frontal gyrus enhances working memory performance,” *Neuroimage*, vol. 184, no. August 2018, pp. 697–706, 2019, doi: 10.1016/j.neuroimage.2018.09.064.
- [134] N. M. Long, J. F. Burke, and M. J. Kahana, “Subsequent memory effect in intracranial and

scalp EEG.,” *Neuroimage*, vol. 84, pp. 488–94, Jan. 2014, doi: 10.1016/j.neuroimage.2013.08.052.

- [135] P. B. Sederberg, M. J. Kahana, M. W. Howard, E. J. Donner, and J. R. Madsen, “Theta and Gamma Oscillations during Encoding Predict Subsequent Recall,” *J. Neurosci.*, vol. 23, no. 34, pp. 10809–10814, Nov. 2003, Accessed: Feb. 29, 2016. [Online]. Available: <http://www.jneurosci.org.myaccess.library.utoronto.ca/content/23/34/10809.long>.
- [136] J. A. Greenberg, J. F. Burke, R. Haque, M. J. Kahana, and K. A. Zaghloul, “Decreases in theta and increases in high frequency activity underlie associative memory encoding.,” *Neuroimage*, vol. 114, pp. 257–63, Jul. 2015, doi: 10.1016/j.neuroimage.2015.03.077.
- [137] S. Guderian, B. H. Schott, A. Richardson-Klavehn, E. Duzel, and E. Düzel, “Medial temporal theta state before an event predicts episodic encoding success in humans,” *Proc. Natl. Acad. Sci.*, vol. 106, no. 13, pp. 5365–5370, Mar. 2009, doi: 10.1073/pnas.0900289106.
- [138] J. Fell *et al.*, “Medial temporal theta/alpha power enhancement precedes successful memory encoding: evidence based on intracranial EEG.,” *J. Neurosci.*, vol. 31, no. 14, pp. 5392–7, Apr. 2011, doi: 10.1523/JNEUROSCI.3668-10.2011.
- [139] M. B. Merkow, J. F. Burke, J. M. Stein, and M. J. Kahana, “Prestimulus theta in the human hippocampus predicts subsequent recognition but not recall.,” *Hippocampus*, vol. 24, no. 12, pp. 1562–9, Dec. 2014, doi: 10.1002/hipo.22335.
- [140] N. E. Crone, A. Korzeniewska, and P. J. Franaszczuk, “Cortical gamma responses: Searching high and low,” *International Journal of Psychophysiology*, vol. 79, no. 1, pp. 9–15, 2011, doi: 10.1016/j.ijpsycho.2010.10.013.
- [141] K. J. Miller *et al.*, “Spectral changes in cortical surface potentials during motor movement.,” *J. Neurosci.*, vol. 27, no. 9, pp. 2424–32, 2007, doi: 10.1523/JNEUROSCI.3886-06.2007.
- [142] K. J. K. J. Miller, *Broadband spectral change: Evidence for a macroscale correlate of*

population firing rate?, vol. 30, no. 19. 2010, pp. 6477–6479.

- [143] U. Rutishauser, I. B. Ross, A. N. Mamelak, and E. M. Schuman, “Human memory strength is predicted by theta-frequency phase-locking of single neurons,” *Nature*, vol. 464, no. 7290, pp. 903–907, 2010, doi: 10.1038/nature08860.
- [144] Y. Ezzyat *et al.*, “Closed-loop stimulation of temporal cortex rescues functional networks and improves memory,” 2018. doi: 10.1038/s41467-017-02753-0.
- [145] D. Song, R. H. M. Chan, V. Z. Marmarelis, R. E. Hampson, S. A. Deadwyler, and T. W. Berger, “Nonlinear dynamic modeling of spike train transformations for hippocampal-cortical prostheses,” *IEEE Trans. Biomed. Eng.*, vol. 54, no. 6, pp. 1053–1066, 2007, doi: 10.1109/TBME.2007.891948.
- [146] D. Song, R. H. M. Chan, V. Z. Marmarelis, R. E. Hampson, S. A. Deadwyler, and T. W. Berger, “Nonlinear modeling of neural population dynamics for hippocampal prostheses,” *Neural Networks*, vol. 22, no. 9, pp. 1340–1351, 2009, doi: 10.1016/j.neunet.2009.05.004.
- [147] R. E. Hampson *et al.*, “Developing a hippocampal neural prosthetic to facilitate human memory encoding and recall,” *J. Neural Eng.*, vol. 15, no. 3, 2018, doi: 10.1088/1741-2552/aaaed7.
- [148] R. J. Molitor, P. C. Ko, E. P. Hussey, and B. A. Ally, “Memory-related eye movements challenge behavioral measures of pattern completion and pattern separation,” *Hippocampus*, vol. 24, no. 6, pp. 666–672, 2014, doi: 10.1002/hipo.22256.
- [149] J. F. Fagan, “Infants’ delayed recognition memory and forgetting,” *J. Exp. Child Psychol.*, vol. 16, no. 3, pp. 424–450, 1973, doi: 10.1016/0022-0965(73)90005-2.
- [150] M. J. Jutras and E. A. Buffalo, “Recognition memory signals in the macaque hippocampus,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 107, no. 1, pp. 401–6, Jan. 2010, doi: 10.1073/pnas.0908378107.
- [151] D. Noton and L. Stark, “Scanpaths in Eye Movements during Pattern Perception,” 1971.

- [152] J. S. Wynn, M. B. Bone, M. C. Dragan, K. L. Hoffman, B. R. Buchsbaum, and J. D. Ryan, “Selective scanpath repetition during memory-guided visual search,” *Vis. cogn.*, vol. 24, no. 1, pp. 15–37, Jan. 2016, doi: 10.1080/13506285.2016.1175531.
- [153] L. Holm and T. Mäntylä, “Memory for scenes: Refixations reflect retrieval,” *Mem. Cogn.*, vol. 35, no. 7, pp. 1664–1674, 2007, doi: 10.3758/BF03193500.
- [154] A. Kafkas and D. Montaldi, “Recognition memory strength is predicted by pupillary responses at encoding while fixation patterns distinguish recollection from familiarity,” *Q. J. Exp. Psychol.*, vol. 64, no. 10, pp. 1971–1989, 2011, doi: 10.1080/17470218.2011.588335.
- [155] I. van der Linde, U. Rajashekar, A. C. Bovik, and L. K. Cormack, “Visual memory for fixated regions of natural images dissociates attraction and recognition,” *Perception*, vol. 38, no. 8, pp. 1152–1171, 2009, doi: 10.1068/p6142.
- [156] J. P. K. Chan, D. Kamino, M. A. Binns, and J. D. Ryan, “Can changes in eye movement scanning alter the age-related deficit in recognition memory?,” *Front. Psychol.*, vol. 2, no. MAY, 2011, doi: 10.3389/fpsyg.2011.00092.
- [157] J. S. Wynn, J. D. Ryan, and B. R. Buchsbaum, “Eye movements support behavioral pattern completion,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 117, no. 11, pp. 6246–6254, Mar. 2020, doi: 10.1073/pnas.1917586117.
- [158] S. M. Stark, M. A. Yassa, J. W. Lacy, and C. E. L. Stark, “A task to assess behavioral pattern separation (BPS) in humans: Data from healthy aging and mild cognitive impairment,” *Neuropsychologia*, vol. 51, no. 12, pp. 2442–2449, Oct. 2013, doi: 10.1016/j.neuropsychologia.2012.12.014.
- [159] J. S. Wynn, K. Shen, and J. D. Ryan, “Eye movements actively reinstate spatiotemporal mnemonic content,” *Vision*, vol. 3, no. 2, pp. 1–19, 2019, doi: 10.3390/vision3020021.
- [160] M. L. R. R. Meister and E. A. Buffalo, “Getting directions from the hippocampus: The neural connection between looking and memory,” *Neurobiol. Learn. Mem.*, vol. 134, pp.

135–144, Dec. 2015, doi: 10.1016/j.nlm.2015.12.004.

- [161] P. Pajkossy, Á. Szöllösi, and M. Racsmány, “Pupil size changes signal hippocampus-related memory functions,” *Sci. Rep.*, vol. 10, no. 1, p. 16393, Dec. 2020, doi: 10.1038/s41598-020-73374-9.
- [162] M. M. Bradley and P. J. Lang, “Memory, emotion, and pupil diameter: Repetition of natural scenes,” *Psychophysiology*, vol. 52, no. 9, pp. 1186–1193, 2015, doi: 10.1111/psyp.12442.
- [163] M. A. Yassa and C. E. L. Stark, “Pattern separation in the hippocampus,” *Trends Cogn. Sci.*, vol. 34, no. 10, pp. 515–525, 2011, doi: 10.1038/jid.2014.371.
- [164] D. J. Felleman and D. C. Van Essen, “Distributed hierarchical processing in the primate cerebral cortex,” *Cereb. Cortex*, vol. 1, no. 1, pp. 1–47, 1991, doi: 10.1093/cercor/1.1.1-a.
- [165] K. Shen, G. Bezgin, R. Selvam, A. R. McIntosh, and J. D. Ryan, “An Anatomical Interface between Memory and Oculomotor Systems,” *J. Cogn. Neurosci.*, vol. 28, no. 11, pp. 1772–1783, 2016, doi: 10.1162/jocn.
- [166] Z.-X. Liu, K. Shen, R. K. Olsen, and J. D. Ryan, “Visual Sampling Predicts Hippocampal Activity,” *J. Neurosci.*, vol. 37, no. 3, pp. 599–609, 2017, doi: 10.1523/JNEUROSCI.2610-16.2017.
- [167] D. E. Hannula and C. Ranganath, “The eyes have it: hippocampal activity predicts expression of memory in eye movements.,” *Neuron*, vol. 63, no. 5, pp. 592–9, 2009, doi: 10.1016/j.neuron.2009.08.025.
- [168] A. J. Ryals, J. X. Wang, K. L. Polnaszek, and J. L. Voss, “Hippocampal contribution to implicit configuration memory expressed via eye movements during scene exploration,” *Hippocampus*, vol. 25, no. 9, pp. 1028–1041, Sep. 2015, doi: 10.1002/hipo.22425.
- [169] F. Taghdiri *et al.*, “Decreased number of self-paced saccades in post-concussion syndrome associated with higher symptom burden and reduced white matter integrity,” *J. Neurotrauma*, vol. 11, p. neu.2017.5274, 2017, doi: 10.1089/neu.2017.5274.

- [170] J. D. Ryan, R. R. Althoff, S. Whitlow, and N. J. Cohen, “Amnesia is a deficit in relational memory.,” *Psychol. Sci. a J. Am. Psychol. Soc. / APS*, vol. 11, no. 6, pp. 454–461, 2000, doi: 10.1111/1467-9280.00288.
- [171] D. E. Hannula, J. D. Ryan, D. Tranel, and N. J. Cohen, “Rapid onset relational memory effects are evident in eye movement behavior, but not in hippocampal amnesia.,” *J. Cogn. Neurosci.*, vol. 19, no. 10, pp. 1690–705, Oct. 2007, doi: 10.1162/jocn.2007.19.10.1690.
- [172] R. K. Olsen *et al.*, “The relationship between eye movements and subsequent recognition: Evidence from individual differences and amnesia,” *Cortex*, vol. 85, pp. 182–193, Dec. 2016, doi: 10.1016/j.cortex.2016.10.007.
- [173] D. J. Mort *et al.*, “The anatomy of visual neglect,” *Brain*, vol. 126, no. 9, pp. 1986–1997, Sep. 2003, doi: 10.1093/brain/awg200.
- [174] C. J. Keller, C. J. Honey, P. Mégevand, L. Entz, I. Ulbert, and A. D. Mehta, “Mapping human brain networks with cortico-cortical evoked potentials.,” *Philos. Trans. R. Soc. Lond. B. Biol. Sci.*, vol. 369, no. 1653, Oct. 2014, doi: 10.1098/rstb.2013.0528.
- [175] P. Mégevand *et al.*, “The Hippocampus and Amygdala Are Integrators of Neocortical Influence: A CorticoCortical Evoked Potential Study,” *Brain Connect.*, vol. 7, no. 10, pp. 648–660, 2017, doi: 10.1089/brain.2017.0527.
- [176] Y. Kubota *et al.*, “In vivo human hippocampal cingulate connectivity: a corticocortical evoked potentials (CCEPs) study.,” *Clin. Neurophysiol.*, vol. 124, no. 8, pp. 1547–56, Aug. 2013, doi: 10.1016/j.clinph.2013.01.024.
- [177] R. Enatsu *et al.*, “Connectivity of the frontal and anterior insular network: a cortico-cortical evoked potential study,” *J Neurosurg*, vol. 125, no. 125, pp. 90–101, 2016, doi: 10.3171/2015.6.JNS15622.
- [178] R. Enatsu *et al.*, “Connections of the limbic network: a corticocortical evoked potentials study.,” *Cortex.*, vol. 62, pp. 20–33, Jan. 2015, doi: 10.1016/j.cortex.2014.06.018.
- [179] S. Sobotka, W. Zuo, and J. L. Ringo, “Is the functional connectivity within temporal lobe

influenced by saccadic eye movements?,” *J. Neurophysiol.*, vol. 88, no. 4, pp. 1675–1684, 2002, doi: 10.1152/jn.2002.88.4.1675.

- [180] A. S. Shah *et al.*, “Neural Dynamics and the Fundamental Mechanisms of Event-related Brain Potentials,” *Cereb. Cortex*, vol. 14, no. 5, pp. 476–483, Mar. 2004, doi: 10.1093/cercor/bhh009.
- [181] C. N. Katz, J. Zariffa, and T. A. Valiante, “Intracranial Electroencephalography (In Press),” in *The Neurotech Primer: A Beginner’s Guide to Everything Neurotechnology*, 2021.
- [182] W. Klimesch, R. Freunberger, P. Sauseng, and W. Gruber, “A short review of slow phase synchronization and memory: Evidence for control processes in different memory systems?,” *Brain Res.*, vol. 1235, pp. 31–44, 2008, doi: 10.1016/j.brainres.2008.06.049.
- [183] B. Voloh and T. Womelsdorf, “A Role of Phase-Resetting in Coordinating Large Scale Neural Networks During Attention and Goal-Directed Behavior.,” *Front. Syst. Neurosci.*, vol. 10, p. 18, 2016, doi: 10.3389/fnsys.2016.00018.
- [184] N. Axmacher, F. Mormann, G. Fernández, C. E. Elger, and J. Fell, “Memory formation by neuronal synchronization,” *Brain Res. Rev.*, vol. 52, no. 1, pp. 170–182, Aug. 2006, doi: 10.1016/j.brainresrev.2006.01.007.
- [185] C. C. Canavier, “Phase-resetting as a tool of information transmission,” *Curr. Opin. Neurobiol.*, vol. 31, pp. 206–213, Apr. 2015, doi: 10.1016/j.conb.2014.12.003.
- [186] W. Buño, J. L. Garcia-Sanchez, and E. Garcia-Austt, “Reset of hippocampal rhythmical activities by afferent stimulation.,” *Brain Res. Bull.*, vol. 3, no. 1, pp. 21–8, 1978, doi: 0361-9230(78)90057-6 [pii] ET - 1978/01/01.
- [187] B. Givens, “Stimulus-evoked resetting of the dentate theta rhythm: relation to working memory.,” *Neuroreport*, vol. 8, no. 1, pp. 159–163, 1996, doi: 10.1097/00001756-199612200-00032.
- [188] J. M. Williams and B. Givens, “Stimulation-induced reset of hippocampal theta in the

- freely performing rat.,” *Hippocampus*, vol. 13, no. 1, pp. 109–16, Jan. 2003, doi: 10.1002/hipo.10082.
- [189] H. McCartney, A. D. Johnson, Z. M. Weil, and B. Givens, “Theta reset produces optimal conditions for long-term potentiation.,” *Hippocampus*, vol. 14, no. 6, pp. 684–7, 2004, doi: 10.1002/hipo.20019.
- [190] J. Fell, E. Ludowig, T. Rosburg, N. Axmacher, and C. E. Elger, “Phase-locking within human mediotemporal lobe predicts memory formation,” *Neuroimage*, vol. 43, no. 2, pp. 410–419, 2008, doi: 10.1016/j.neuroimage.2008.07.021.
- [191] G. Fernandez, A. Effern, T. Grunwald, and N. Pezer, “Real-Time Tracking of Memory Formation in the Human Rhinal Cortex and Hippocampus,” *Science*, vol. 285, no. 1999, pp. 1582–1585, 1999, doi: 10.1126/science.285.5433.1582.
- [192] C. D. Tesche and J. Karhu, “Theta oscillations index human hippocampal activation during a working memory task,” *Proc. Natl. Acad. Sci.*, vol. 97, no. 2, pp. 919–924, Jan. 2000, doi: 10.1073/pnas.97.2.919.
- [193] S. Raghavachari, J. E. Lisman, M. Tully, J. R. Madsen, E. B. Bromfield, and M. J. Kahana, “Theta oscillations in human cortex during a working-memory task: evidence for local generators.,” *J. Neurophysiol.*, vol. 95, no. 3, pp. 1630–1638, 2006, doi: 10.1152/jn.00409.2005.
- [194] K. A. Paller and G. McCarthy, “Field potentials in the human hippocampus during the encoding and recognition of visual stimuli,” *Hippocampus*, vol. 12, no. 3, pp. 415–420, 2002, doi: 10.1002/hipo.10053.
- [195] T. Staudigl, E. Hartl, S. Noachtar, C. F. Doeller, and O. Jensen, “Saccades phase-locked to alpha oscillations in the occipital and medial temporal lobe enhance memory encoding,” *PLoS Biol.*, vol. 15, pp. 1–15, 2017, doi: 10.1101/158758.
- [196] J. E. Kragel *et al.*, “Hippocampal theta coordinates memory processing during visual exploration,” *Elife*, vol. 9, Mar. 2020, doi: 10.7554/eLife.52108.

- [197] F. Mormann *et al.*, “Phase/amplitude reset and theta-gamma interaction in the human medial temporal lobe during a continuous word recognition memory task,” *Hippocampus*, vol. 15, no. 7, pp. 890–900, Jan. 2005, doi: 10.1002/hipo.20117.
- [198] M. J. Jutras, P. Fries, and E. A. Buffalo, “Oscillatory activity in the monkey hippocampus during visual exploration and memory formation.,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 110, no. 32, pp. 13144–9, Aug. 2013, doi: 10.1073/pnas.1302351110.
- [199] K. L. Hoffman, M. C. Dragan, T. K. Leonard, C. Micheli, R. Montefusco-Siegmund, and T. A. Valiante, “Saccades during visual exploration align hippocampal 3-8 Hz rhythms in human and non-human primates.,” *Front. Syst. Neurosci.*, vol. 7, no. August, p. 43, Jan. 2013, doi: 10.3389/fnsys.2013.00043.
- [200] G. Buzsáki, “Theta Oscillations in the Hippocampus,” *Neuron*, vol. 33, no. 3, pp. 325–340, Jan. 2002, doi: 10.1016/S0896-6273(02)00586-X.
- [201] P. T. Huerta and J. E. Lisman, “Synaptic Plasticity During the Cholinergic Theta-Frequency Oscillation In Vitro,” *Hippocampus*, vol. 61, no. 1936, pp. 58–61, 1996.
- [202] J. H. Siegle and M. A. Wilson, “Enhancement of encoding and retrieval functions through theta phase-specific manipulation of hippocampus,” *Elife*, vol. 2014, no. 3, pp. 1–18, 2014, doi: 10.7554/eLife.03061.001.
- [203] M. E. Hasselmo, “What is the function of hippocampal theta rhythm?—Linking behavioral data to phasic properties of field potential and unit recording data,” *Hippocampus*, vol. 15, no. 7, pp. 936–949, 2005, doi: 10.1002/hipo.20116.
- [204] M. E. Hasselmo, C. Bodelón, and B. P. Wyble, “A proposed function for hippocampal theta rhythm: separate phases of encoding and retrieval enhance reversal of prior learning.,” *Neural Comput.*, vol. 14, no. 4, pp. 793–817, May 2002, doi: 10.1162/089976602317318965.
- [205] M. E. Hasselmo and C. E. Stern, “Theta rhythm and the encoding and retrieval of space and time,” *Neuroimage*, vol. 85, no. 0 2, pp. 656–666, 2014, doi:

10.1016/j.neuroimage.2013.06.022.

- [206] J. R. Manns, E. A. Zilli, K. C. Ong, M. E. Hasselmo, and H. Eichenbaum, “Hippocampal CA1 spiking during encoding and retrieval: Relation to theta phase,” *Neurobiol. Learn. Mem.*, vol. 87, no. 1, pp. 9–20, 2007, doi: 10.1016/j.nlm.2006.05.007.
- [207] G. Buzsáki *et al.*, “Laminar Distribution of Hippocampal Rhythmic Slow Activity (RSA) in the Behaving Rat: Current-Source Density Analysis, Effects of Urethane and Atropine,” *Brain Res.*, vol. 365, no. 1, pp. 125–137, Feb. 1986, doi: 10.1016/0006-8993(86)90729-8.
- [208] J. Brankack, M. Stewart, S. E. Fox, J. Brankačk, M. Stewart, and S. E. Fox, “Current source density analysis of the hippocampal theta rhythm: associated sustained potentials and candidate synaptic generators,” *Brain Res.*, vol. 615, no. 2, pp. 310–327, Jul. 1993, doi: 10.1016/0006-8993(93)90043-M.
- [209] E. W. Schomburg *et al.*, “Theta Phase Segregation of Input-Specific Gamma Patterns in Entorhinal-Hippocampal Networks,” *Neuron*, vol. 84, no. 2, pp. 470–485, 2014, doi: 10.1016/j.neuron.2014.08.051.
- [210] L. L. Colgin *et al.*, “Frequency of gamma oscillations routes flow of information in the hippocampus,” *Nature*, vol. 462, no. 7271, pp. 353–7, Nov. 2009, doi: 10.1038/nature08573.
- [211] K. Mizuseki, A. Sirota, E. Pastalkova, and G. Buzsáki, “Theta Oscillations Provide Temporal Windows for Local Circuit Computation in the Entorhinal-Hippocampal Loop,” *Neuron*, vol. 64, no. 2, pp. 267–280, 2009, doi: 10.1016/j.neuron.2009.08.037.
- [212] P. T. Huerta and J. E. Lisman, “Low-frequency stimulation at the troughs of theta-oscillation induces long-term depression of previously potentiated CA1 synapses,” *J. Neurophysiol.*, vol. 75, no. 2, pp. 877–884, 1996.
- [213] D. Bush *et al.*, “Human hippocampal theta power indicates movement onset and distance travelled,” *Proc. Natl. Acad. Sci.*, 2017, doi: 10.1073/pnas.1708716114.
- [214] Z. M. Aghajani *et al.*, “Theta Oscillations in the Human Medial Temporal Lobe during

- Real-World Ambulatory Movement,” *Curr. Biol.*, vol. 27, no. 24, pp. 3743-3751.e3, 2017, doi: 10.1016/j.cub.2017.10.062.
- [215] M. Stewart and S. E. Fox, “Hippocampal theta activity in monkeys,” *Brain Res.*, vol. 538, no. 1, pp. 59–63, Jan. 1991, doi: 10.1016/0006-8993(91)90376-7.
- [216] C. N. Katz, K. Patel, O. Talakoub, D. Groppe, K. L. Hoffman, and T. A. Valiante, “Differential Generation of Saccade, Fixation, and Image-Onset Event-Related Potentials in the Human Mesial Temporal Lobe,” *Cereb. Cortex*, vol. 30, no. 10, pp. 5502–5516, 2020, doi: 10.1093/cercor/bhaa132.
- [217] P. B. Sederberg *et al.*, “Hippocampal and Neocortical Gamma Oscillations Predict Memory Formation in Humans,” *Cereb. Cortex*, vol. 17, no. 5, pp. 1190–1196, 2006, doi: 10.1093/cercor/bhl030.
- [218] R. Montefusco-Siegmund, T. K. Leonard, and K. L. Hoffman, “Hippocampal gamma-band Synchrony and pupillary responses index memory during visual search,” *Hippocampus*, vol. 27, no. 4, pp. 425–434, 2017, doi: 10.1002/hipo.22702.
- [219] J. Fell *et al.*, “Neural Bases of Cognitive ERPs: More than Phase Reset,” *J. Cogn. Neurosci.*, vol. 16, no. 9, pp. 1595–1604, Nov. 2004, doi: 10.1162/0898929042568514.
- [220] M. L. R. Meister and E. A. Buffalo, “Neurobiology of Learning and Memory Getting directions from the hippocampus : The neural connection between looking and memory,” *Neurobiol. Learn. Mem.*, vol. 134, pp. 135–144, 2016, doi: 10.1016/j.nlm.2015.12.004.
- [221] T. Andrillon, Y. Nir, C. Cirelli, G. Tononi, and I. Fried, “Single-neuron activity and eye movements during human REM sleep and awake vision,” *Nat. Commun.*, vol. 6, p. 7884, Aug. 2015, doi: 10.1038/ncomms8884.
- [222] H. G. Rey *et al.*, “Single-cell recordings in the human medial temporal lobe,” *J. Anat.*, vol. 227, no. 4, pp. 394–408, 2015, doi: 10.1111/joa.12228.
- [223] M. S. Beauchamp, K. E. Lee, B. D. Argall, and A. Martin, “Integration of Auditory and Visual Information about Objects in Superior Temporal Sulcus,” *Neuron*, vol. 41, no. 5,

pp. 809–823, 2004, doi: 10.1016/S0896-6273(04)00070-4.

- [224] A. M. Bartlett, S. Ovaysikia, N. K. Logothetis, and K. L. Hoffman, “Saccades during object viewing modulate oscillatory phase in the superior temporal sulcus.,” *J. Neurosci.*, vol. 31, no. 50, pp. 18423–32, Dec. 2011, doi: 10.1523/JNEUROSCI.4102-11.2011.
- [225] T. B. Crapse and M. A. Sommer, “Corollary discharge across the animal kingdom,” *Nat. Rev. Neurosci.*, vol. 9, no. august, pp. 587–600, 2008, doi: 10.1038/nrn2457.
- [226] M. A. Sommer and R. H. Wurtz, “A Pathway in Primate Brain for Internal Monitoring of Movements,” *Science*, vol. 296, no. 5772, pp. 1480–1482, 2002, doi: 10.1126/science.1069590.
- [227] K. P. Purpura, S. F. Kalik, and N. D. Schiff, “Analysis of Perisaccadic Field Potentials in the Occipitotemporal Pathway During Active Vision,” *J. Neurophysiol.*, vol. 90, no. 5, pp. 3455–3478, 2003, doi: 10.1152/jn.00011.2003.
- [228] J. K. Kleen *et al.*, “Oscillation Phase Locking and Late ERP Components of Intracranial Hippocampal Recordings Correlate to Patient Performance in a Working Memory Task,” *Front. Hum. Neurosci.*, vol. 10, no. June, pp. 1–14, 2016, doi: 10.3389/fnhum.2016.00287.
- [229] N. Axmacher *et al.*, “Intracranial EEG correlates of expectancy and memory formation in the human hippocampus and nucleus accumbens.,” *Neuron*, vol. 65, no. 4, pp. 541–9, Feb. 2010, doi: 10.1016/j.neuron.2010.02.006.
- [230] C. McCormick, M. St-Laurent, A. Ty, T. A. Valiante, and M. P. McAndrews, “Functional and effective hippocampal-neocortical connectivity during construction and elaboration of autobiographical memory retrieval.,” *Cereb. Cortex*, vol. 25, no. 5, pp. 1297–305, May 2015, doi: 10.1093/cercor/bht324.
- [231] J. Brewer, Z. Zhao, J. Desmond, G. Glover, and J. D. Gabrieli, “Making Memories: Brain Activity that Predicts How Well Visual Experience Will Be Remembered,” *Science*, vol. 281, pp. 1185–1187, 1998, doi: 10.1126/science.281.5380.1185.

- [232] O. Jackson and D. L. Schacter, “Encoding activity in anterior medial temporal lobe supports subsequent associative recognition,” *Neuroimage*, vol. 21, no. 1, pp. 456–462, 2004, doi: 10.1016/j.neuroimage.2003.09.050.
- [233] M. B. Merkow, J. F. Burke, and M. J. Kahana, “The human hippocampus contributes to both the recollection and familiarity components of recognition memory.,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 112, no. 46, pp. 14378–83, Nov. 2015, doi: 10.1073/pnas.1513145112.
- [234] E. L. Johnson and R. T. Knight, “Intracranial recordings and human memory,” *Curr. Opin. Neurobiol.*, vol. 31, pp. 18–25, 2015, doi: 10.1016/j.conb.2014.07.021.
- [235] P. Davis, “Effects of acoustic stimuli on the waking human brain,” *J. Neurophysiol.*, vol. 2, pp. 494–499, 1939, doi: <https://doi.org/10.1152/jn.1939.2.6.494>.
- [236] W. Klimesch, S. Hanslmayr, P. Sauseng, and W. R. Gruber, “Distinguishing the evoked response from phase reset: A comment to Mäkinen et al.,” *Neuroimage*, vol. 29, no. 3, pp. 808–811, 2006, doi: 10.1016/j.neuroimage.2005.08.041.
- [237] S. Hanslmayr *et al.*, “Alpha phase reset contributes to the generation of ERPs,” *Cereb. Cortex*, vol. 17, no. 1, pp. 1–8, 2007, doi: 10.1093/cercor/bhj129.
- [238] T. Womelsdorf, T. A. Valiante, N. T. Sahin, K. J. Miller, and P. Tiesinga, “Dynamic circuit motifs underlying rhythmic gain control, gating and integration,” *Nat. Neurosci.*, vol. 17, no. 8, pp. 1031–1039, 2014, doi: 10.1038/nn.3764.
- [239] P. Sauseng, W. Klimesch, W. R. Gruber, S. Hanslmayr, R. Freunberger, and M. Doppelmayr, “Are event-related potential components generated by phase resetting of brain oscillations? A critical discussion.,” *Neuroscience*, vol. 146, no. 4, pp. 1435–44, Jun. 2007, doi: 10.1016/j.neuroscience.2007.03.014.
- [240] S. Makeig *et al.*, “Dynamic Brain Sources of Visual Evoked Responses,” *Science*, vol. 295, no. 5555, pp. 690–694, 2002, Accessed: Aug. 27, 2017. [Online]. Available: <http://science.sciencemag.org/content/295/5555/690.full>.

- [241] S. M. Sherman and R. W. Guillery, “The role of the thalamus in the flow of information to the cortex,” *Philos. Trans. R. Soc. B Biol. Sci.*, vol. 357, no. 1428, pp. 1695–1708, 2002, doi: 10.1098/rstb.2002.1161.
- [242] C. E. Schroeder and P. Lakatos, “Low-frequency neuronal oscillations as instruments of sensory selection,” *Trends Neurosci.*, vol. 32, no. 1, pp. 9–18, 2010, doi: 10.1016/j.tins.2008.09.012.Low-frequency.
- [243] V. L. Chau, E. F. Murphy, R. S. Rosenbaum, J. D. Ryan, and K. L. Hoffman, “A Flicker Change Detection Task Reveals Object-in-Scene Memory Across Species.,” *Front. Behav. Neurosci.*, vol. 5, p. 58, Jan. 2011, doi: 10.3389/fnbeh.2011.00058.
- [244] D. D. Salvucci and J. H. Goldberg, “Identifying fixations and saccades in eye-tracking protocols,” in *Proceedings of the symposium on Eye tracking research & applications - ETRA '00*, 2000, no. October, pp. 71–78, doi: 10.1145/355017.355028.
- [245] R. Andersson, L. Larsson, K. Holmqvist, M. Stridh, and M. Nyström, “One algorithm to rule them all? An evaluation and discussion of ten eye movement event-detection algorithms,” *Behav. Res. Methods*, vol. 49, no. 2, pp. 616–637, 2017, doi: 10.3758/s13428-016-0738-9.
- [246] D. M. Groppe *et al.*, “iELVis: An open source MATLAB toolbox for localizing and visualizing human intracranial electrode data,” *J. Neurosci. Methods*, vol. 281, pp. 40–48, Apr. 2017, doi: 10.1016/j.jneumeth.2017.01.022.
- [247] C. K. Kovach, N. Tsuchiya, H. Kawasaki, H. Oya, M. A. Howard, and R. Adolphs, “Manifestation of ocular-muscle EMG contamination in human intracranial recordings,” *Neuroimage*, vol. 54, no. 1, pp. 213–233, 2011, doi: 10.1016/j.neuroimage.2010.08.002.
- [248] K. Jerbi *et al.*, “Saccade related gamma-band activity in intracerebral EEG: Dissociating neural from ocular muscle activity,” *Brain Topogr.*, vol. 22, no. 1, pp. 18–23, 2009, doi: 10.1007/s10548-009-0078-5.
- [249] A. J. Bell and T. J. Sejnowski, “An Information-Maximization Approach to Blind

Separation and Blind Deconvolution,” *Neural Comput.*, vol. 7, no. 6, pp. 1129–1159, 1995, doi: 10.1162/neco.1995.7.6.1129.

- [250] A. Delorme and S. Makeig, “EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis,” *J. Neurosci. Methods*, vol. 134, no. 1, pp. 9–21, 2004, doi: 10.1016/j.jneumeth.2003.10.009.
- [251] T. J. Abel *et al.*, “Beta modulation reflects name retrieval in the human anterior temporal lobe: an intracranial recording study,” *J. Neurophysiol.*, vol. 115, no. 6, pp. 3052–3061, 2016, doi: 10.1152/jn.00012.2016.
- [252] J. W. Tukey, *Exploratory Data Analysis*, vol. 2, no. 1999. Reading, Massachusetts-Menlo Park, California- London- Amsterdam - Don Mills, Ontario - Sydney: Addison-Wesley Publishing Company, 1977.
- [253] T. K. Leonard *et al.*, “Sharp Wave Ripples during Visual Exploration in the Primate Hippocampus,” *J. Neurosci.*, vol. 35, no. 44, pp. 14771–14782, Nov. 2015, doi: 10.1523/JNEUROSCI.0864-15.2015.
- [254] T. K. Leonard and K. L. Hoffman, “Sharp-Wave Ripples in Primates Are Enhanced near Remembered Visual Objects,” *Curr. Biol.*, vol. 27, no. 2, pp. 257–262, 2017, doi: 10.1016/j.cub.2016.11.027.
- [255] B. W. Corrigan, R. A. Gulli, G. Doucet, and J. C. Martinez-Trujillo, “Characterizing Eye Movement Behaviors and Kinematics of Non-Human Primates During Virtual Navigation Tasks,” *J. Vis.*, vol. 17, no. 15, pp. 1–22, 2017, doi: 10.1167/17.12.15.doi.
- [256] S. Yuval-Greenberg, O. Tomer, A. S. Keren, I. Nelken, and L. Y. Deouell, “Transient Induced Gamma-Band Response in EEG as a Manifestation of Miniature Saccades,” *Neuron*, vol. 58, no. 3, pp. 429–441, 2008, doi: 10.1016/j.neuron.2008.03.027.
- [257] M. A. Kramer, A. B. L. Tort, and N. J. Kopell, “Sharp edge artifacts and spurious coupling in EEG frequency comodulation measures,” *J. Neurosci. Methods*, vol. 170, no. 2, pp. 352–357, 2008, doi: 10.1016/j.jneumeth.2008.01.020.

- [258] C. G. Bénar, L. Chauvière, F. Bartolomei, and F. Wendling, “Pitfalls of high-pass filtering for detecting epileptic oscillations: A technical note on ‘false’ ripples,” *Clin. Neurophysiol.*, vol. 121, no. 3, pp. 301–310, 2010, doi: 10.1016/j.clinph.2009.10.019.
- [259] B. A. Lopour, A. Tavassoli, I. Fried, and D. L. Ringach, “Coding of information in the phase of local field potentials within human medial temporal lobe,” *Neuron*, vol. 79, no. 3, pp. 594–606, Aug. 2013, doi: 10.1016/j.neuron.2013.06.001.
- [260] F. Mormann, G. Fernández, P. Klaver, B. Weber, C. E. Elger, and J. Fell, “Declarative memory formation in hippocampal sclerosis: an intracranial event-related potentials study.,” *Neuroreport*, vol. 18, no. 4, pp. 317–21, 2007, doi: 10.1097/WNR.0b013e3280287ae9.
- [261] Niemeyer P., “The transventricular amygdalohippocampectomy in temporal lobe epilepsy,” in *M. Baldwin, P. Bailey (Eds.), Temporal Lobe Epilepsy, Charles C. Thomas, Springfield, Ill (1958)*, 1958, pp. 461–482.
- [262] S. Musall *et al.*, “Effects of neural synchrony on surface EEG,” *Cereb. Cortex*, vol. 24, no. 4, pp. 1045–1053, 2014, doi: 10.1093/cercor/bhs389.
- [263] F. Mormann *et al.*, “Scene-selective coding by single neurons in the human parahippocampal cortex,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 114, no. 5, pp. 1153–1158, Jan. 2017, doi: 10.1073/pnas.1608159113.
- [264] C. Rajkai, P. Lakatos, C. M. Chen, Z. Pincze, G. Karmos, and C. E. Schroeder, “Transient cortical excitation at the onset of visual fixation,” *Cereb. Cortex*, vol. 18, no. 1, pp. 200–209, 2008, doi: 10.1093/cercor/bhm046.
- [265] C. M. Hamamé *et al.*, “Functional selectivity in the human occipitotemporal cortex during natural vision: Evidence from combined intracranial EEG and eye-tracking,” *Neuroimage*, vol. 95, pp. 276–286, 2014, doi: 10.1016/j.neuroimage.2014.03.025.
- [266] J. Ito, P. Maldonado, W. Singer, S. Grun, and S. Grün, “Saccade-Related Modulations of Neuronal Excitability Support Synchrony of Visually Elicited Spikes,” *Cereb. Cortex*, vol.

21, no. 11, pp. 2482–2497, Nov. 2011, doi: 10.1093/cercor/bhr020.

- [267] M. A. Sommer and R. H. Wurtz, “Brain Circuits for the Internal Monitoring of Movements,” *Annu. Rev. Neurosci.*, vol. 31, no. 1, pp. 317–338, 2008, doi: 10.1146/annurev.neuro.31.060407.125627.
- [268] N. J. Killian, S. M. Potter, and E. A. Buffalo, “Saccade direction encoding in the primate entorhinal cortex during visual exploration,” *Proc. Natl. Acad. Sci.*, vol. 112, pp. 15743–15748, 2015, doi: 10.1073/pnas.1417059112.
- [269] J.-R. R. Duhamel, C. L. Colby, and M. E. Goldberg, “The updating of the representation of visual space in parietal cortex by intended eye movements,” *Science*, vol. 255, no. 5040, pp. 90–92, Jan. 1992, doi: 10.1126/science.1553535.
- [270] F. P. Battaglia, K. Benchenane, A. Sirota, C. M. a Pennartz, and S. I. Wiener, “The hippocampus: Hub of brain network communication for memory,” *Trends Cogn. Sci.*, vol. 15, no. 7, pp. 310–318, 2011, doi: 10.1016/j.tics.2011.05.008.
- [271] S. Sobotka and J. L. Ringo, “Saccadic eye movements, even in darkness, generate event-related potentials recorded in medial sputum and medial temporal cortex.,” *Brain Res.*, vol. 756, no. 1–2, pp. 168–173, 1997, doi: 10.1016/S0006-8993(97)00145-5.
- [272] J. L. Ringo, S. Sobotka, M. D. Diltz, and C. M. Bunce, “Eye movements modulate activity in hippocampal, parahippocampal, and inferotemporal neurons,” *J. Neurophysiol.*, vol. 71, no. 3, pp. 1285–1288, 1994, doi: 10.1152/jn.1994.71.3.1285.
- [273] O. S. Vinogradova, “Hippocampus as Comparator: Role of the Two Input and Two Output Systems of the Hippocampus in Selection and Registration of Information,” *Hippocampus*, vol. 72, no. 11, pp. 1285–1286, 2008, doi: 10.1101/112268.
- [274] R. L. Buckner, “The role of the hippocampus in prediction and imagination.,” *Annu. Rev. Psychol.*, vol. 61, pp. 27–48, C1–C8, 2010, doi: 10.1146/annurev.psych.60.110707.163508.
- [275] L. M. Grover, E. Kim, J. D. Cooke, and W. R. Holmes, “LTP in hippocampal area CA1 is

induced by burst stimulation over a broad frequency range centered around delta.,” *Learn. Mem.*, vol. 16, no. 1, pp. 69–81, Jan. 2009, doi: 10.1101/lm.1179109.

- [276] S. Nemanic, M. C. Alvarado, and J. Bachevalier, “The Hippocampal/Parahippocampal Regions and Recognition Memory: Insights from Visual Paired Comparison versus Object-Delayed Nonmatching in Monkeys,” *J. Neurosci.*, vol. 24, no. 8, pp. 2013–2026, 2004, doi: 10.1523/JNEUROSCI.3763-03.2004.
- [277] C. A. Anastassiou, R. Perin, H. Markram, and C. Koch, “Ephaptic coupling of cortical neurons,” in *Nature Neuroscience*, 2011, vol. 14, no. 2, pp. 217–224, doi: 10.1038/nn.2727.
- [278] S. R. Cobb, E. H. Buhl, K. Halasy, O. Paulsen, and P. Somogyi, “Synchronization of neuronal activity in hippocampus by individual GABAergic interneurons,” *Nature*, vol. 378, pp. 75–78, 1995, doi: 10.1038/378075a0.
- [279] G. Buzsáki, C. a. Anastassiou, and C. Koch, “The origin of extracellular fields and currents — EEG, ECoG, LFP and spikes,” *Nat. Rev. Neurosci.*, vol. 13, no. 6, pp. 407–420, 2012, doi: 10.1038/nrn3241.
- [280] M. W. Reimann, C. A. Anastassiou, R. Perin, S. L. Hill, H. Markram, and C. Koch, “A biophysically detailed model of neocortical local field potentials predicts the critical role of active membrane currents,” *Neuron*, vol. 79, pp. 375–390, 2013, doi: 10.1016/j.neuron.2013.05.023.
- [281] B. Haider, D. P. P. A. Schulz, M. Häusser, and M. Carandini, “Millisecond Coupling of Local Field Potentials to Synaptic Currents in the Awake Visual Cortex,” *Neuron*, vol. 90, no. 1, pp. 35–42, 2016, doi: 10.1016/j.neuron.2016.02.034.
- [282] M. Yoshida, E. Fransén, and M. E. Hasselmo, “mGluR-dependent persistent firing in entorhinal cortex layer III neurons,” *Eur. J. Neurosci.*, vol. 28, no. 6, pp. 1116–1126, 2008, doi: 10.1111/j.1460-9568.2008.06409.x.
- [283] J. Suh, A. J. Rivest, T. Nakashiba, T. Tominaga, and S. Tonegawa, “Entorhinal cortex

layer III input to the hippocampus is crucial for temporal association memory,” *Science*, vol. 334, no. 6061, pp. 1415–1420, Dec. 2011, doi: 10.1126/science.1210125.

- [284] D. G. Amaral and M. P. Witter, “The three-dimensional organization of the hippocampal formation: A review of anatomical data,” *Neuroscience*, vol. 31, no. 3, pp. 571–591, 1989, doi: 10.1016/0306-4522(89)90424-7.
- [285] C. N. Katz *et al.*, “A corollary discharge mediates saccade related inhibition of single units in mnemonic structures of the human brain,” *bioRxiv*, p. 2021.07.12.450085, Jul. 2021, doi: 10.1101/2021.07.12.450085.
- [286] E. T. Rolls and S. Wirth, “Spatial representations in the primate hippocampus, and their functions in memory and navigation,” *Prog. Neurobiol.*, vol. 171, no. September, pp. 90–113, 2018, doi: 10.1016/j.pneurobio.2018.09.004.
- [287] A. D. Ekstrom, “Why vision is important to how we navigate,” *Hippocampus*. 2015, doi: 10.1002/hipo.22449.
- [288] C. E. Schroeder, D. Wilson, T. Radman, H. E. Scharfman, and P. Lakatos, “Dynamics of Active Sensing and Perceptual Selection Charles,” *Curr. Opin. Neurobiol.*, vol. 20, no. 2, pp. 172–176, 2010, doi: 10.1016/j.conb.2010.02.010.Dynamics.
- [289] R. K. Olsen, M. Chiew, B. R. Buchsbaum, and J. D. Ryan, “The relationship between delay period eye movements and visuospatial memory,” *J. Vis.*, vol. 14, no. 1, pp. 1–11, 2014, doi: 10.1167/14.1.8.doi.
- [290] S. A. Yoo, R. S. Rosenbaum, J. K. Tsotsos, M. Fallah, and K. L. Hoffman, “Long-term memory and hippocampal function support predictive gaze control during goal-directed search,” *J. Vis.*, vol. 20, no. 5, pp. 1–14, 2020, doi: 10.1167/jov.20.5.10.
- [291] T. B. Crapse and M. A. Sommer, “Corollary discharge circuits in the primate brain,” *Curr. Opin. Neurobiol.*, vol. 18, no. 6, pp. 552–557, 2008, doi: 10.1016/j.conb.2008.09.017.
- [292] B. J. Richmond and R. H. Wurtz, “Vision during saccadic eye movements. II. A corollary discharge to monkey superior colliculus,” *J. Neurophysiol.*, vol. 43, no. 4, pp. 1156–67,

1980, doi: 10.1152/jn.1980.43.4.1156.

- [293] D. L. Robinson and R. H. Wurtz, “Use of an extraretinal signal by monkey superior colliculus neurons to distinguish real from self induced stimulus movement,” *J. Neurophysiol.*, vol. 39, no. 4, pp. 852–870, 1976, doi: 10.1152/jn.1976.39.4.852.
- [294] R. A. Berman, J. Cavanaugh, K. McAlonan, and R. H. Wurtz, “A circuit for saccadic suppression in the primate brain,” *J. Neurophysiol.*, vol. 117, no. 4, pp. 1720–1735, 2017, doi: 10.1152/jn.00679.2016.
- [295] S. Idrees, M. P. Baumann, F. Franke, T. A. Münch, and Z. M. Hafed, “Perceptual saccadic suppression starts in the retina,” doi: 10.1038/s41467-020-15890-w.
- [296] R. H. Wurtz, “Corollary Discharge Contributions to Perceptual Continuity Across Saccades,” *Annu. Rev. Vis. Sci.*, vol. 4, no. 1, pp. 215–237, 2018, doi: 10.1146/annurev-vision-102016-061207.
- [297] J. Cavanaugh, R. A. Berman, W. M. Joiner, and R. H. Wurtz, “Saccadic Corollary Discharge Underlies Stable Visual Perception,” *J. Neurosci.*, vol. 36, no. 1, pp. 31–42, 2016, doi: 10.1523/jneurosci.2054-15.2016.
- [298] N. J. Killian, M. J. Jutras, and E. A. Buffalo, “A map of visual space in the primate entorhinal cortex,” *Nature*, vol. 491, no. 7426, pp. 761–4, Nov. 2012, doi: 10.1038/nature11587.
- [299] R. H. Wurtz and M. A. Sommer, “Identifying corollary discharges for movement in the primate brain,” *Prog. Brain Res.*, vol. 144, pp. 47–60, 2004, doi: 10.1016/S0079-6123(03)14403-2.
- [300] M. A. Sommer and R. H. Wurtz, “A pathway in primate brain for internal monitoring of movements,” *Science*, vol. 296, no. 5572, pp. 1480–1482, 2002, doi: 10.1126/science.1069590.
- [301] S. Kornblith *et al.*, “Persistent Single-Neuron Activity during Working Memory in the Human Medial Temporal Lobe,” *Curr. Biol.*, vol. 27, no. 7, pp. 1026–1032, 2017, doi:

10.1016/j.cub.2017.02.013.

- [302] F. Mormann *et al.*, “Latency and Selectivity of Single Neurons Indicate Hierarchical Processing in the Human Medial Temporal Lobe,” *J Neurosci*, vol. 28, no. 36, pp. 8865–8872, 2008, doi: 10.1523/JNEUROSCI.1640-08.2008.Latency.
- [303] R. Quian Quiroga, L. Reddy, G. Kreiman, C. Koch, and I. Fried, “Invariant visual representation by single neurons in the human brain,” *Nature*, vol. 435, no. 7045, pp. 1102–1107, 2005, doi: 10.1038/nature03687.
- [304] M. C. M. Faraut *et al.*, “Dataset of human medial temporal lobe single neuron activity during declarative memory encoding and recognition,” *Sci. Data*, vol. 5, p. 180010, 2018, doi: 10.1038/sdata.2018.10.
- [305] U. Rutishauser, E. M. Schuman, and A. N. Mamelak, “Online detection and sorting of extracellularly recorded action potentials in human medial temporal lobe recordings, in vivo,” *J. Neurosci. Methods*, vol. 154, no. 1–2, pp. 204–224, 2006, doi: 10.1016/j.jneumeth.2005.12.033.
- [306] N. Chandravadia *et al.*, “A NWB-based dataset and processing pipeline of human single-neuron activity during a declarative memory task,” *Sci. Data*, vol. 7, no. 1, pp. 1–12, Dec. 2020, doi: 10.1038/s41597-020-0415-9.
- [307] K. Patel, C. N. Katz, S. K. Kalia, M. R. Popovic, and T. Valiante, “Volitional Control of Individual Neurons in the Human Brain,” *bioRxiv*, 2020, doi: 10.1101/2020.05.05.079038.
- [308] J. F. Mitchell, K. A. Sundberg, and J. H. Reynolds, “Differential Attention-Dependent Response Modulation across Cell Classes in Macaque Visual Area V4,” *Neuron*, 2007, doi: 10.1016/j.neuron.2007.06.018.
- [309] Z. Fu *et al.*, “Single-Neuron Correlates of Error Monitoring and Post-Error Adjustments in Human Medial Frontal Cortex,” *Neuron*, 2019, doi: 10.1016/j.neuron.2018.11.016.
- [310] U. Rutishauser *et al.*, “Representation of retrieval confidence by single neurons in the human medial temporal lobe,” *Nat. Neurosci.*, vol. 18, no. 7, pp. 1041–1050, Jun. 2015,

doi: 10.1016/j.ygyno.2014.12.035.Pharmacologic.

- [311] M. A. Sommer and R. H. Wurtz, “Influence of the thalamus on spatial visual processing in frontal cortex,” *Nature*, vol. 444, no. 7117, pp. 374–377, 2006, doi: 10.1038/nature05279.
- [312] G. Doucet, R. A. Gulli, B. W. Corrigan, L. R. Duong, and J. C. Martinez-Trujillo, “Modulation of local field potentials and neuronal activity in primate hippocampus during saccades,” *Hippocampus*, no. December 2018, pp. 1–18, 2019, doi: 10.1002/hipo.23140.
- [313] K. S. LaBar and R. Cabeza, “Cognitive neuroscience of emotional memory,” *Nat. Rev. Neurosci.*, vol. 7, no. 1, pp. 54–64, 2006, doi: 10.1038/nrn1825.
- [314] A. Caputi, S. Melzer, M. Michael, and H. Monyer, “The long and short of GABAergic neurons,” *Current Opinion in Neurobiology*, vol. 23, no. 2. Elsevier Current Trends, pp. 179–186, Apr. 01, 2013, doi: 10.1016/j.conb.2013.01.021.
- [315] R. A. Gulli *et al.*, “Context-dependent representations of objects and space in the primate hippocampus during virtual navigation,” *Nat. Neurosci.*, vol. 23, no. January, 2020, doi: 10.1038/s41593-019-0548-3.
- [316] J. D. Green and A. A. Arduini, “Hippocampal electrical activity in arousal.,” *J. Neurophysiol.*, vol. 17, no. 6, pp. 533–57, Nov. 1954.
- [317] O. S. S. Vinogradova, “Expression, control, and probable functional significance of the neuronal theta-rhythm,” *Prog. Neurobiol.*, vol. 45, no. 6, pp. 523–583, Apr. 1995, doi: 10.1016/0301-0082(94)00051-I.
- [318] M. B. Zugaro, L. Monconduit, and G. Buzsáki, “Spike phase precession persists after transient intrahippocampal perturbation.,” *Nat. Neurosci.*, vol. 8, no. 1, pp. 67–71, 2005, doi: 10.1038/nn1369.
- [319] D. E. Hannula, R. R. Althoff, D. E. Warren, L. Riggs, N. J. Cohen, and J. D. Ryan, “Worth a glance: using eye movements to investigate the cognitive neuroscience of memory.,” *Front. Hum. Neurosci.*, vol. 4, p. 166, 2010, doi: 10.3389/fnhum.2010.00166.

- [320] J. D. Ryan, K. Shen, and Z. X. Liu, “The intersection between the oculomotor and hippocampal memory systems: empirical developments and clinical implications,” *Ann. N. Y. Acad. Sci.*, vol. 1464, no. 1, pp. 115–141, 2020, doi: 10.1111/nyas.14256.
- [321] G. D. Horwitz and W. T. Newsome, “Target selection for saccadic eye movements: prelude activity in the superior colliculus during a direction-discrimination task.,” *J. Neurophysiol.*, vol. 86, no. 5, pp. 2543–58, 2001, [Online]. Available: <http://www.ncbi.nlm.nih.gov/pubmed/11698541>.
- [322] L. Pessoa and R. Adolphs, “Emotion processing and the amygdala: from a ‘low road’ to ‘many roads’ of evaluating biological significance.,” *Nat. Rev. Neurosci.*, vol. 11, no. 11, pp. 773–783, 2010, doi: 10.1038/nrn2920.
- [323] M. M. Jankowski *et al.*, “Nucleus reuniens of the thalamus contains head direction cells.,” *Elife*, vol. 3, p. e03075, Jan. 2014, doi: 10.7554/eLife.03075.
- [324] M. J. Dolleman-Van der Weel, F. H. Lopes da Silva, and M. P. Witter, “Nucleus reuniens thalami modulates activity in hippocampal field CA1 through excitatory and inhibitory mechanisms.,” *J. Neurosci.*, vol. 17, no. 14, pp. 5640–50, Jul. 1997.
- [325] M. J. Dolleman-Van der Weel and M. P. Witter, “Nucleus reuniens thalami innervates gamma aminobutyric acid positive cells in hippocampal field CA1 of the rat.,” *Neurosci. Lett.*, vol. 278, no. 3, pp. 145–8, Jan. 2000.
- [326] M. J. Dolleman-Van Der Weel *et al.*, “The nucleus reuniens of the thalamus sits at the nexus of a hippocampus and medial prefrontal cortex circuit enabling memory and behavior,” *Learning and Memory*, vol. 26, no. 7. Cold Spring Harbor Laboratory Press, pp. 191–205, 2019, doi: 10.1101/lm.048389.118.
- [327] M. J. Dolleman-Van Der Weel and M. P. Witter, “Projections from the nucleus reuniens thalami to the entorhinal cortex, hippocampal field CA1, and the subiculum in the rat arise from different populations of neurons.,” *J. Comp. Neurol.*, vol. 364, no. 4, pp. 637–50, Jan. 1996, doi: 10.1002/(SICI)1096-9861(19960122)364:4<637::AID-CNE3>3.0.CO;2-4.

- [328] J. O'Keefe and J. Dostrovsky, "The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat," *Brain Res.*, vol. 34, no. 1, pp. 171–175, 1971, doi: 10.1016/0006-8993(71)90358-1.
- [329] R. A. Epstein, E. Z. Patai, J. B. Julian, and H. J. Spiers, "The cognitive map in humans: Spatial navigation and beyond," *Nat. Neurosci.*, vol. 20, no. 11, pp. 1504–1513, 2017, doi: 10.1038/nn.4656.
- [330] T. Hafting, M. Fyhn, S. Molden, M.-B. Moser, and E. I. Moser, "Microstructure of a spatial map in the entorhinal cortex.," *Nature*, vol. 436, no. 7052, pp. 801–6, 2005, doi: 10.1038/nature03721.
- [331] F. Sargolini *et al.*, "Conjunctive representation of position, direction, and velocity in entorhinal cortex," *Science (80-.)*, 2006, doi: 10.1126/science.1125572.
- [332] W. M. Joiner, J. Cavanaugh, E. J. FitzGibbon, and R. H. Wurtz, "Corollary discharge contributes to perceived eye location in monkeys," *J. Neurophysiol.*, vol. 110, no. 10, pp. 2402–2413, 2013, doi: 10.1152/jn.00362.2013.
- [333] G. Buzsáki and E. I. Moser, "Memory, navigation and theta rhythm in the hippocampal-entorhinal system.," *Nat. Neurosci.*, vol. 16, no. 2, pp. 130–8, Feb. 2013, doi: 10.1038/nn.3304.
- [334] G. Buzsáki, *Rhythms of the Brain*. Oxford University Press, 2006.
- [335] G. Maccaferri and R. Dingledine, "Control of feedforward dendritic inhibition by NMDA receptor-dependent spike timing in hippocampal interneurons," *J. Neurosci.*, 2002, doi: 10.1523/jneurosci.22-13-05462.2002.
- [336] E. Tulving, "Memory and Consciousness," *Can. Psychol.*, vol. 26, no. 1, pp. 1–12, 1985.
- [337] J. M. Henderson, C. C. Williams, and R. J. Falk, "Eye movements are functional during face learning," *Mem. Cognit.*, vol. 33, no. 1, pp. 98–106, Jan. 2005, doi: 10.3758/BF03195300.

- [338] B. Fehlmann *et al.*, “Visual Exploration at Higher Fixation Frequency Increases Subsequent Memory Recall,” *Cereb. Cortex Commun.*, vol. 1, no. 1, pp. 1–14, Aug. 2020, doi: 10.1093/texcom/tgaa032.
- [339] S. J. Katarina Slama *et al.*, “Intracranial recordings demonstrate medial temporal lobe engagement in visual search in humans,” *bioRxiv*, 2020, doi: 10.1101/2020.02.29.971341.
- [340] G. Buzsáki, “Theta rhythm of navigation: Link between path integration and landmark navigation, episodic and semantic memory,” *Hippocampus*, vol. 15, no. 7, pp. 827–840, 2005, doi: 10.1002/hipo.20113.
- [341] N. A. Herweg, E. A. Solomon, and M. J. Kahana, “Theta Oscillations in Human Memory,” *Trends Cogn. Sci.*, pp. 1–20, 2019, doi: 10.1016/j.tics.2019.12.006.
- [342] M. S. Nokia, T. Waselius, J. E. Mikkonen, J. Wikgren, and M. Penttonen, “Phase matters: responding to and learning about peripheral stimuli depends on hippocampal θ phase at stimulus onset,” *Learn. Mem.*, vol. 22, no. 6, pp. 307–317, 2015, doi: 10.1101/lm.038166.115.
- [343] E. Maris and R. Oostenveld, “Nonparametric statistical testing of EEG- and MEG-data,” *J. Neurosci. Methods*, vol. 164, no. 1, pp. 177–190, 2007, doi: 10.1016/j.jneumeth.2007.03.024.
- [344] O. Talakoub, A. Gomez Palacio Schjetnan, T. A. Valiante, M. R. Popovic, and K. L. Hoffman, “Closed-Loop Interruption of Hippocampal Ripples through Fornix Stimulation in the Non-Human Primate,” *Brain Stimul.*, vol. 9, no. 6, pp. 911–918, Nov. 2016, doi: 10.1016/j.brs.2016.07.010.
- [345] B. Zhou, A. Lapedriza, A. Khosla, A. Oliva, and A. Torralba, “Places: A 10 Million Image Database for Scene Recognition,” *IEEE Trans. Pattern Anal. Mach. Intell.*, vol. 40, no. 6, pp. 1452–1464, 2018, doi: 10.1109/TPAMI.2017.2723009.
- [346] Z. Wang and A. Bovik, “A universal image quality index,” *IEEE Signal Process. Lett.*, vol. 9, no. 3, pp. 81–84, 2002, doi: 10.1109/97.995823.

- [347] Z. Wang, A. C. Bovik, H. R. Sheikh, and E. P. Simoncelli, “Image quality assessment: From error visibility to structural similarity,” *IEEE Trans. Image Process.*, vol. 13, no. 4, pp. 600–612, 2004, doi: 10.1109/TIP.2003.819861.
- [348] C. J. Lin *et al.*, “Developing and Evaluating a Target-Background Similarity Metric for Camouflage Detection,” *PLoS One*, vol. 9, no. 2, p. e87310, Feb. 2014, doi: 10.1371/journal.pone.0087310.
- [349] D. Bates, M. Mächler, B. Bolker, and S. Walker, “Fitting Linear Mixed-Effects Models using lme4,” *J. Stat. Softw.*, no. 1, 2014, doi: 10.18637/jss.v067.i01.
- [350] N. Suthana, Z. M. Aghajan, E. A. Mankin, and A. Lin, “Reporting Guidelines and Issues to Consider for Using Intracranial Brain Stimulation in Studies of Human Declarative Memory,” *Front. Neurosci.*, vol. 12, no. December, 2018, doi: 10.3389/fnins.2018.00905.
- [351] A. Goyal *et al.*, “Electrical stimulation in hippocampus and entorhinal cortex impairs spatial and temporal memory,” *J. Neurosci.*, vol. 38, no. 19, pp. 3049–17, 2018, doi: 10.1523/JNEUROSCI.3049-17.2018.
- [352] L. L. Colgin, “Do slow and fast gamma rhythms correspond to distinct functional states in the hippocampal network?,” *Brain Res.*, no. 1621, pp. 309–315, 2015, doi: 10.1016/j.brainres.2015.01.005.Do.
- [353] A. Bragin, G. Jandó, Z. Nádasdy, J. Hetke, K. Wise, and G. Buzsáki, “Gamma (40-100 Hz) oscillation in the hippocampus of the behaving rat,” *J. Neurosci.*, vol. 15, no. 1 I, pp. 47–60, 1995, doi: 10.1523/jneurosci.15-01-00047.1995.
- [354] F. Mansouri, K. Dunlop, P. Giacobbe, J. Downar, and J. Zariffa, “A fast EEG forecasting algorithm for phase-locked transcranial electrical stimulation of the human brain,” *Front. Neurosci.*, vol. 11, no. JUL, pp. 1–14, 2017, doi: 10.3389/fnins.2017.00401.
- [355] J. B. Ranck, “WHICH ELEMENTS ARE EXCITED IN ELECTRICAL STIMULATION OF MAMMALIAN CENTRAL NERVOUS SYSTEM: A REVIEW,” *Brain Res.*, vol. 98, pp. 417–440, 1975.

- [356] E. Kocabicak, Y. Temel, A. Höllig, B. Falkenburger, and S. K. Tan, “Current perspectives on deep brain stimulation for severe neurological and psychiatric disorders.,” *Neuropsychiatr. Dis. Treat.*, vol. 11, pp. 1051–66, Jan. 2015, doi: 10.2147/NDT.S46583.
- [357] A. W. Laxton and A. M. Lozano, “Deep brain stimulation for the treatment of alzheimer disease and dementias,” *World Neurosurg.*, vol. 80, no. 3–4, p. S28.e1-S28.e8, 2013, doi: 10.1016/j.wneu.2012.06.028.
- [358] E. A. Mankin and I. Fried, “Modulation of Human Memory by Deep Brain Stimulation of the Entorhinal-Hippocampal Circuitry,” *Neuron*, vol. 106, no. 2, pp. 218–235, 2020, doi: 10.1016/j.neuron.2020.02.024.
- [359] R. E. Hampson *et al.*, “Developing a hippocampal neural prosthetic to facilitate human memory encoding and recall Facilitation of memory encoding in primate hippocampus by a neuroprosthesis that promotes task-specific neural firing Facilitation and restoration of cognitive funct,” *J. Neural Eng.*, vol. 15, 2018, doi: <https://doi.org/10.1088/1741-2552/aaaed7>.
- [360] D. S. Rizzuto *et al.*, “Reset of human neocortical oscillations during a working memory task.,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 100, no. 13, pp. 7931–6, Jun. 2003, doi: 10.1073/pnas.0732061100.
- [361] J.-J. J. Lin *et al.*, “Theta band power increases in the posterior hippocampus predict successful episodic memory encoding in humans,” *Hippocampus*, vol. 27, no. 10, pp. 1040–1053, Jun. 2017, doi: 10.1002/hipo.22751.
- [362] L. Nadel and M. A. Peterson, “The hippocampus: Part of an interactive posterior representational system spanning perceptual and memorial systems,” *J. Exp. Psychol. Gen.*, vol. 142, no. 4, pp. 1242–1254, 2013, doi: 10.1037/a0033690.
- [363] P. Mégevand *et al.*, “The hippocampus and amygdala are integrators of neocortical influence: a cortico-cortical evoked potential study,” *Brain Connect.*, vol. ahead of p, no. 10, p. brain.2017.0527, 2017, doi: 10.1089/brain.2017.0527.

- [364] M. Moscovitch, R. Cabeza, G. Winocur, and L. Nadel, “Episodic Memory and Beyond: The Hippocampus and Neocortex in Transformation,” *Annu. Rev. Psychol.*, vol. 67, no. 1, pp. 105–134, 2016, doi: 10.1111/obr.12065.Variation.
- [365] J. Jackson, C. T. Dickson, and B. H. Bland, “Median Raphe Stimulation Disrupts Hippocampal Theta Via Rapid Inhibition and State-Dependent Phase Reset of Theta-Related Neural Circuitry,” *J. Neurophysiol.*, vol. 99, no. 6, pp. 3009–3026, 2008, doi: 10.1152/jn.00065.2008.
- [366] C. Drieu and M. Zugaro, “Hippocampal sequences during exploration: Mechanisms and functions,” *Front. Cell. Neurosci.*, vol. 13, no. June, pp. 1–22, 2019, doi: 10.3389/fncel.2019.00232.
- [367] J. O’Keefe and M. L. Recce, “Phase relationship between hippocampal place units and the EEG theta rhythm.,” *Hippocampus*, vol. 3, no. 3, pp. 317–330, Jul. 1993, doi: 10.1002/hipo.450030307.
- [368] S. E. Qasim, I. Fried, and J. Jacobs, “Phase precession in the human hippocampus and entorhinal cortex,” *Preprint*, 2020.
- [369] D. Aronov, R. Nevers, and D. W. Tank, “Mapping of a non-spatial dimension by the hippocampal/entorhinal circuit,” *Nature*, vol. 543, no. 7647, pp. 719–722, 2017, doi: 10.1002/cncr.27633.Percutaneous.
- [370] a D. Ekstrom *et al.*, “Cellular networks underlying human spatial navigation,” *Nature*, vol. 425, no. 6954, pp. 184–188, 2003, doi: 10.1038/nature01955.1.
- [371] J. F. Miller *et al.*, “Neural activity in human hippocampal formation reveals the spatial context of retrieved memories,” *Science (80-.)*, vol. 342, no. 6162, pp. 1111–1114, 2013, doi: 10.1126/science.1244056.
- [372] Z. Nadasdy *et al.*, “Context-dependent spatially periodic activity in the human entorhinal cortex,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 114, no. 17, pp. E3516–E3525, 2017, doi: 10.1073/pnas.1701352114.

- [373] D. Schonhaut, A. Ramayya, E. Solomon, N. Herweg, I. Fried, and M. Kahana, “Single neurons throughout human memory regions phase-lock to hippocampal theta,” 2020, doi: 10.1101/2020.06.30.180174.
- [374] P. Lakatos, M. N. O’Connell, A. Barczak, A. Mills, D. C. Javitt, and C. E. Schroeder, “The Leading Sense: Supramodal Control of Neurophysiological Context by Attention,” *Neuron*, vol. 64, no. 3, pp. 419–430, 2009, doi: 10.1016/j.neuron.2009.10.014.
- [375] M. Leszczynski and C. E. Schroeder, “The Role of Neuronal Oscillations in Visual Active Sensing,” *Front. Integr. Neurosci.*, vol. 13, no. July, pp. 1–9, 2019, doi: 10.3389/fnint.2019.00032.
- [376] A. Barczak, S. Haegens, D. A. Ross, T. McGinnis, P. Lakatos, and C. E. Schroeder, “Dynamic Modulation of Cortical Excitability during Visual Active Sensing,” *Cell Rep.*, vol. 27, no. 12, pp. 3447–3459.e3, 2019, doi: 10.1016/j.celrep.2019.05.072.
- [377] B. C. Lega, J. Jacobs, and M. Kahana, “Human hippocampal theta oscillations and the formation of episodic memories.,” *Hippocampus*, vol. 22, no. 4, pp. 748–61, Apr. 2012, doi: 10.1002/hipo.20937.
- [378] A. Goyal *et al.*, “Functionally distinct high and low theta oscillations in the human hippocampus,” *Nat. Commun.*, vol. 11, no. 1, pp. 1–10, 2020, doi: 10.1038/s41467-020-15670-6.
- [379] G. Pezzulo, C. Kemere, and M. A. A. van der Meer, “Internally generated hippocampal sequences as a vantage point to probe future-oriented cognition,” *Ann. N. Y. Acad. Sci.*, vol. 1396, no. 1, pp. 144–165, 2017, doi: 10.1111/nyas.13329.
- [380] J. Jacobs, “Hippocampal theta oscillations are slower in humans than in rodents: implications for models of spatial navigation and memory.,” *Philos. Trans. R. Soc. Lond. B. Biol. Sci.*, vol. 369, no. 1635, p. 20130304, Feb. 2014, doi: 10.1098/rstb.2013.0304.
- [381] R. Malassis, A. Del Cul, and T. Collins, “Corollary discharge failure in an oculomotor task is related to delusional ideation in healthy Individuals,” *PLoS One*, vol. 10, no. 8, pp.

1–15, 2015, doi: 10.1371/journal.pone.0134483.

- [382] J. Joutsa, E. Eeronheimo, V. Kaasinen, H. Railo, O. Pääkkönen, and H. Olkonieni, “Dopamine and eye movement control in Parkinson’s disease: deficits in corollary discharge signals?,” *PeerJ*, vol. 6, p. e6038, 2018, doi: 10.7717/peerj.6038.
- [383] J. Wang, X. Guo, X. Zhuang, T. Chen, and W. Yan, “Disrupted pursuit compensation during self-motion perception in early Alzheimer’s disease,” *Sci. Rep.*, vol. 7, no. 1, pp. 1–6, 2017, doi: 10.1038/s41598-017-04377-2.
- [384] D. Munoz *et al.*, “Using eye tracking to identify pupil and saccade biomarkers of neurodegenerative disease,” *Neurodegener. Dis.*, 2017.
- [385] A. Peltsch, A. Hemraj, A. Garcia, and D. P. Munoz, “Saccade deficits in amnesic mild cognitive impairment resemble mild Alzheimer’s disease,” *Eur. J. Neurosci.*, 2014, doi: 10.1111/ejn.12617.
- [386] Y. Z. Huang, M. J. Edwards, E. Rounis, K. P. Bhatia, and J. C. Rothwell, “Theta burst stimulation of the human motor cortex,” *Neuron*, vol. 45, no. 2, pp. 201–206, Jan. 2005, doi: 10.1016/j.neuron.2004.12.033.
- [387] I. Feinberg, “efference copy and corollary discharge: implications for thinking and its disorders,” *Schizophr. Bull.*, vol. 4, no. 4, pp. 636–640, 1978, [Online]. Available: [file:///localhost/Users/kuperberglab/Desktop/Gina_sente_library.sente6lib/Contents/Attachments/Feinberg, I/1978/Feinberg Schizophrenia bulletin 197.pdf](file:///localhost/Users/kuperberglab/Desktop/Gina_sente_library.sente6lib/Contents/Attachments/Feinberg_I/1978/Feinberg_Schizophrenia_bulletin_197.pdf).
- [388] A. P. Yonelinas, C. Ranganath, A. D. Ekstrom, and B. J. Wiltgen, “A contextual binding theory of episodic memory: systems consolidation reconsidered,” *Nat. Rev. Neurosci.*, vol. 20, no. 6, pp. 364–375, 2019, doi: 10.1038/s41583-019-0150-4.
- [389] G. Buzsaki, P. Rappelsberger, and L. Kellenyi, “Depth Profiles of Hippocampal Rhythmic Slow Activity (‘Theta Rhythm’) Depend on Behaviour,” *Electroencephalograpt Clin. Neurophysiol.*, vol. 61, pp. 77–88, 1985.

8 Appendices

8.1 Appendix A- Supplementary Items Chapter 3

8.1.1 Figure S1

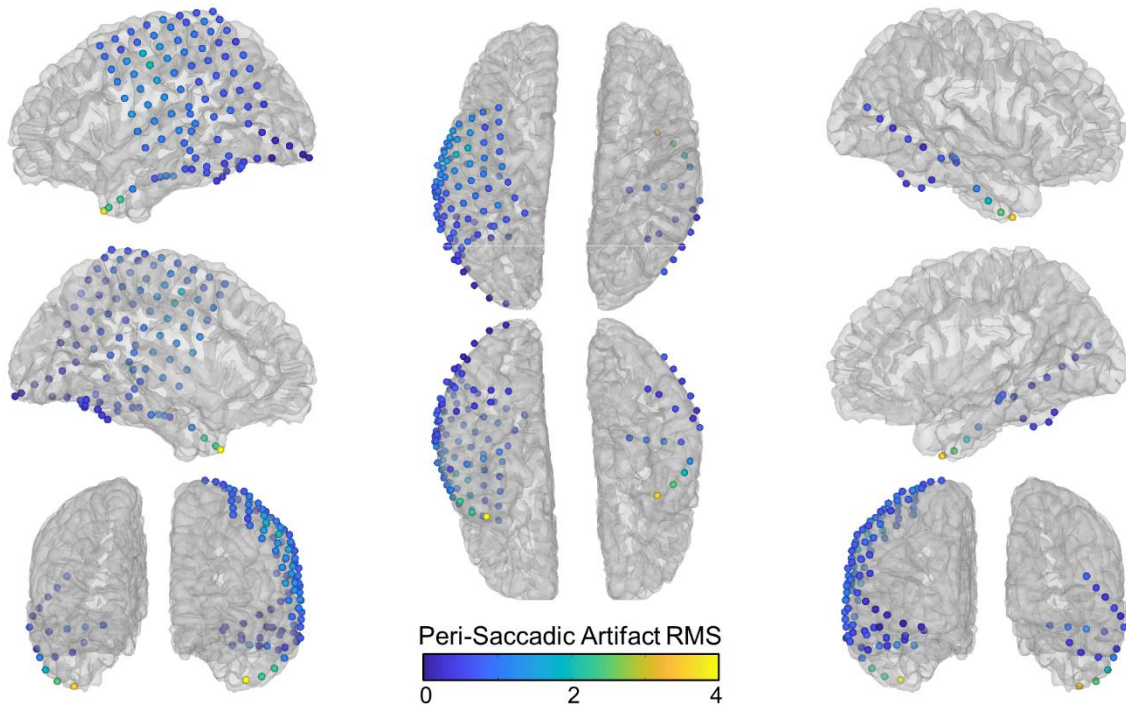


Figure S8.1 Representative distribution of peri-saccadic artifact magnitude: Illustrated is the magnitude of the peri-saccadic artifact across all implanted electrodes for a representative subject. Each circle represents an implanted electrode (grid electrode or depth electrode) overlaid onto the pial surface of the brain and the colour of each circle represents the root-mean-squared (RMS) amplitude of the normalized ERP in a time 40ms time window centered at saccade onset. Notice that the peri-saccadic artifact magnitude is largest (warmest colour) at the electrodes located at the temporal poles and decreases as the electrodes move farther away from the orbit. This suggests that the peri-saccadic artifact is likely the result of volume conduction of a potential generated through the muscle activity associated with ballistic eye movements (electro-oculogram – EOG).

8.1.2 Figure S2

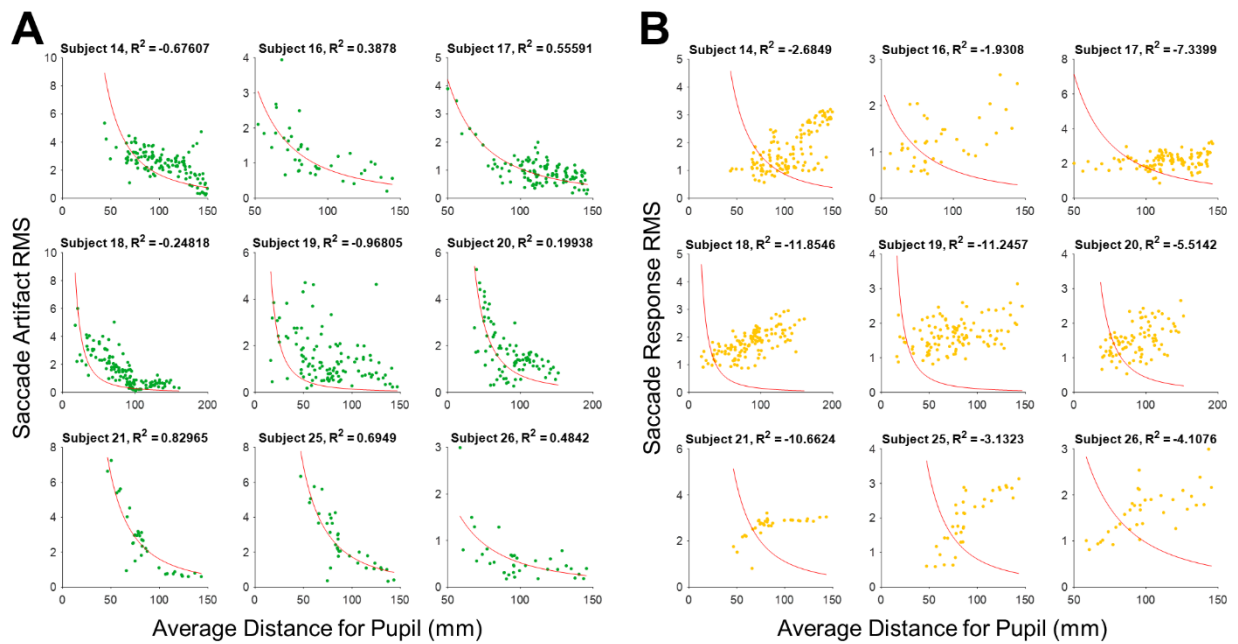


Figure S8.2 | Spatial distribution of peri-saccadic artifact and saccade-onset response magnitude: Plotted are the RMS amplitude of the peri-saccadic artifact A) and the saccade onset response B) across all the electrodes in 9 different subjects. Each plot has been fitted with a power function with an exponent of -2, to model the exponential decay of volume conduction with distance. Note that the peri-saccadic artifact response decays exponentially with distance from the eyes whereas the saccade-onset response does not follow such a relationship. Note that the RMS values are calculated in the same manner as for Figure S1, with a saccade artifact RMS value calculated from a 40ms window surrounding saccade onset and the saccade-onset response RMS value calculated from a window 30-300ms following saccade onset. Some of the R2 values are negative since a constant term was not included in the fitting equation, and suggest that the fit was worse than using horizontal trendline at the sample mean.

8.1.3 Figure S3

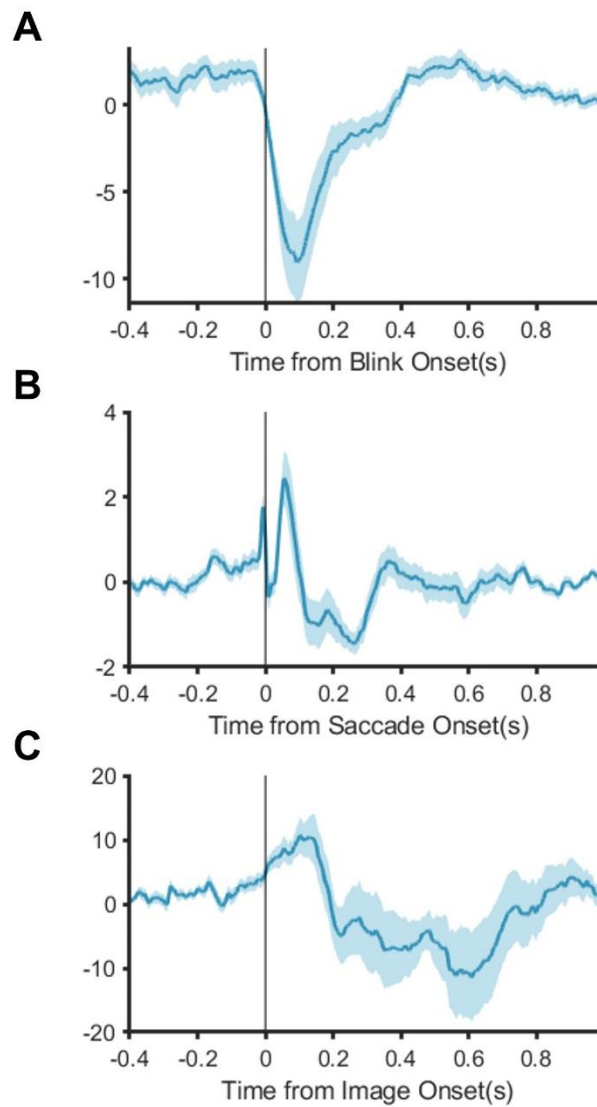


Figure S8.3 | Event-related potentials (ERPs) for blinks: Grand average hippocampal ERP aligned to (A) blink onset, (B) saccade onset and (C) image onset. Blink ERPs were characterized by a large trough ~100ms following blink onset and had a markedly distinct waveform when compared to the saccade or image-onset ERPs in amplitude, timing and polarity. Note that the ocular perisaccadic artifact is not present in the blink ERPs.

8.1.4 Figure S4

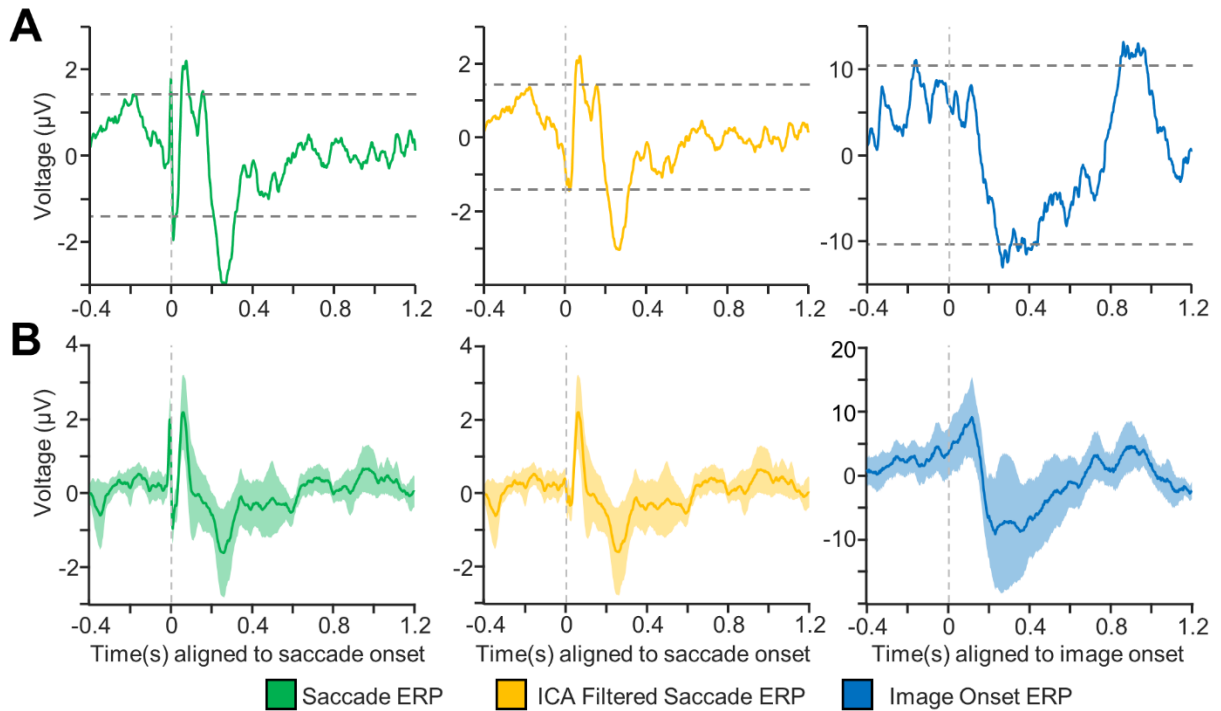


Figure S8.4 | Event-related potentials (ERPs) for parahippocampal electrodes: A) Representative ERPs from a parahippocampal electrode for saccade aligned epochs (left), saccade aligned ICA-filtered epochs (middle) and image-onset aligned epochs (right). The dashed horizontal lines mark significance bounds generated using permutation testing (3000 permutations) with randomized polarity inversions (see Method Details). B) Grand average ERPs for original saccade epochs (left), ICA-filtered saccade epochs (middle) and image-onset (right) ERPs. Note that the saccade onset and image onset response for the parahippocampal electrodes looks very similar to the hippocampal electrode response that is shown in Figure 3.

8.1.5 Figure S5

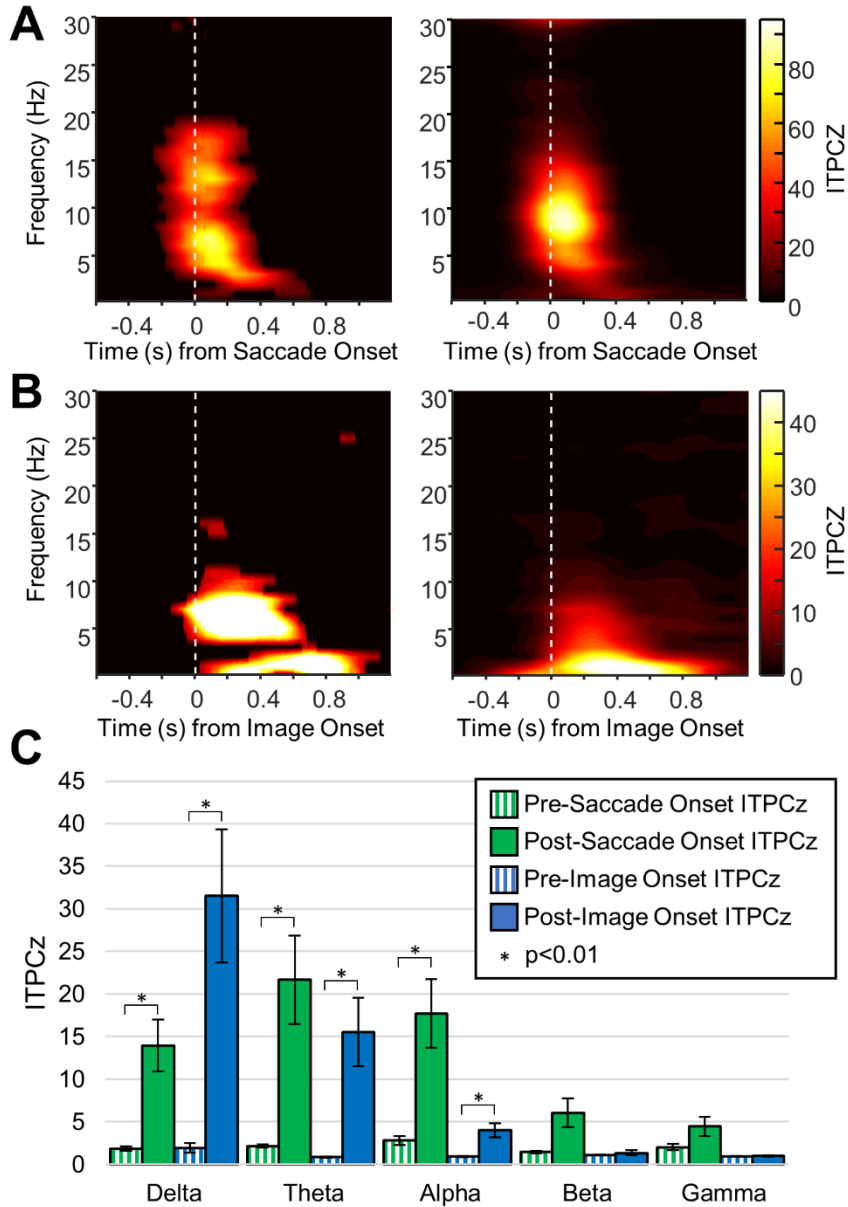


Figure S8.5 | Intertrial phase clustering (ITPC) for saccade onset and image onset for parahippocampal electrodes: A) Left - ITPCz values (ITPC values that have been normalized to Rayleigh's Z to control for a number of trials) for ICA-filtered saccade-aligned epochs, for a representative parahippocampal electrode. The plot has been masked to indicate significant values obtained using a Von-Mises distribution, which has been corrected for multiple comparisons using FDR correction at the $\alpha < 0.001$ significance level (see

Methods). **Right** – Grand average ITPCz value for ICA-filtered saccade aligned epochs for all parahippocampal electrodes. Note the obvious phase clustering in the delta, theta and alpha frequency bands. Also, note that the phase clustering in the theta and alpha frequency bands appears to be stronger in the parahippocampal electrodes compared to the hippocampal electrode phase clustering shown in Figure 5. **B)** Same as A but for image onset aligned epochs for the same representative electrode. Notice that the phase clustering is limited to lower frequency bands and has a longer time course. **C)** Comparison of ITPCz values for different time-frequency windows in the pre and post event periods (see Methods and Table 2 for the definition of these time-frequency windows). Differences in the pre vs. post period were tested for significance using paired T-tests and corrected for multiple comparisons using FDR correction at the $\alpha < 0.01$ significance level. Significant differences are marked with an asterix.

8.1.6 Figure S6

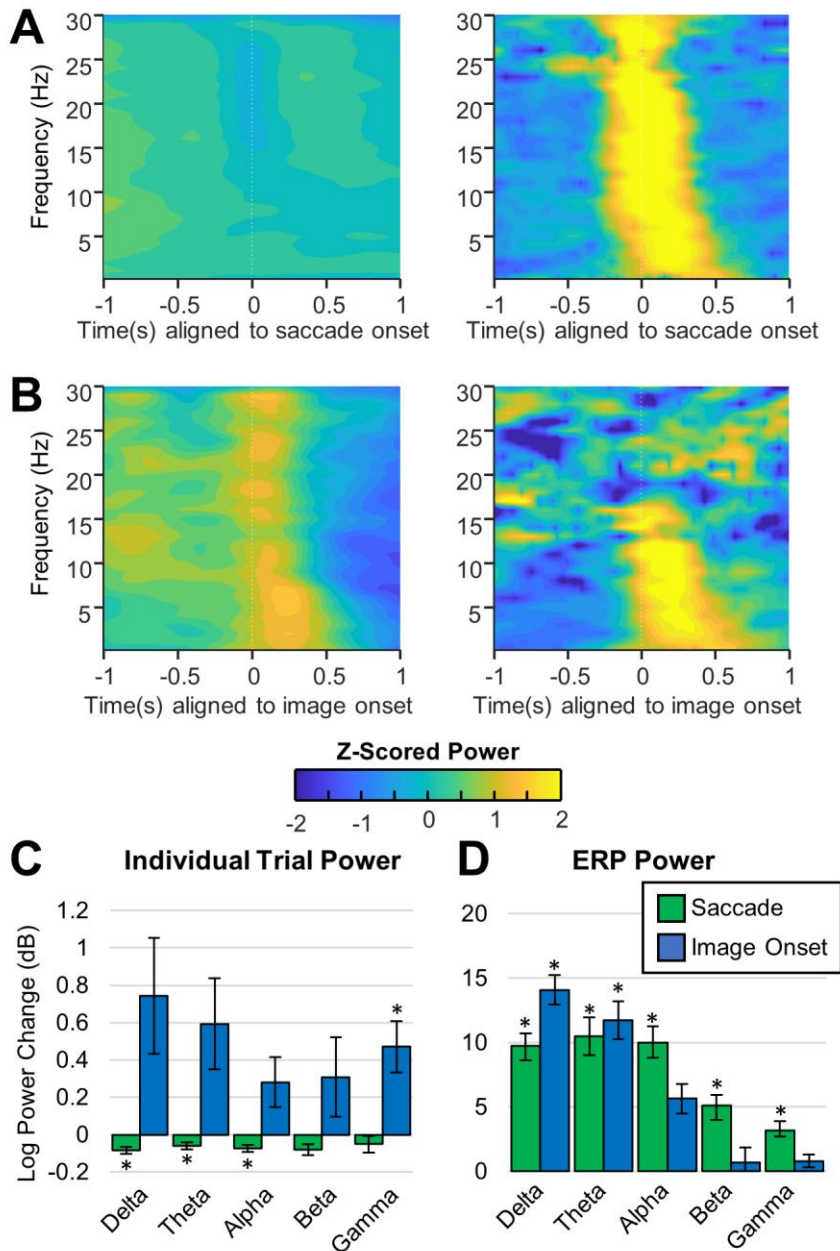


Figure S8.6 | Spectral power for saccade-onset and image-onset epochs for parahippocampal electrodes: A & B show power spectrograms in which the power for each frequency has been z-scored to better visualize power changes within each frequency. A: Left: Average Power of ICA-filtered individual saccade aligned epochs across all parahippocampal electrodes. Right: Average power of ICA-filtered saccade-aligned ERPs averaged across all parahippocampal electrodes. Notice that despite the significant increase in broadband power observed in the saccade ERPs, there is no observable increase in power in the individual trials. B: Left: Average power of individual image-onset aligned epochs across all parahippocampal electrodes. Right: Power

of image-onset aligned ERPs averaged across all parahippocampal electrodes. Note that there is an observable increase in delta-band and theta-band power in the ERP and in the individual trials following image onset. C) Average log power change between pre and post-event time-frequency windows (see Methods for the definition of the time-frequency windows). Notice that there is no significant change in the power following saccade onset, but there is a visible but non-significant increase in the power of the individual trials in the delta and theta bands following image onset. D) same as C but for the power of the ERP. Note that in the ERPs, there is a significant increase in broadband power following saccade onset and a significant increase in lower frequency power (delta and theta) following image onset. Also, note that the power change in the ERP follows a pattern similar to that of the hippocampal electrodes as shown in Figure 6D. Significant changes in power are tested using a paired T-test, corrected for multiple comparisons using FDR correction (see Method Details for more information).

8.1.7 Figure S7

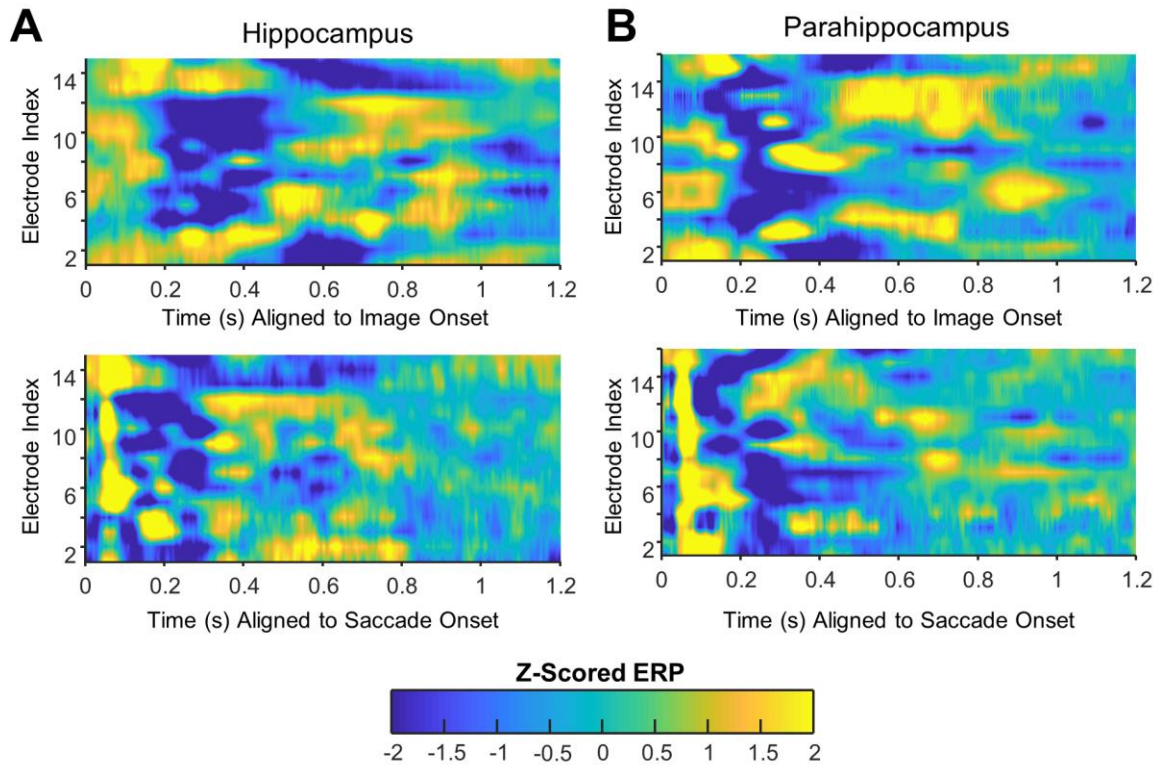


Figure S8.7 | Consistency of ERP for saccade onset and image onset across different trials: Contour plots showing the normalized ERP for all hippocampal (A) and parahippocampal (B) electrodes for image onset (top) and saccade-onset (bottom) aligned data. Note the periodicity in all the responses and the consistency in the first few peaks and troughs of the response. In particular, the first peak of the saccade-onset ERPs occurs around 50ms for all the electrodes across the hippocampus and parahippocampus. Also note that the image onset response has a consistent trough in 200-500ms range. There are however variations in temporal specificity of response within individual electrodes, again possible due to placement or averaging over all events. Qualitatively saccade response starts to dissipate after about 500ms while image onset continues until about 1 second.

8.2 Appendix B- Supplementary Items Chapter 4

8.2.1 Figure S1

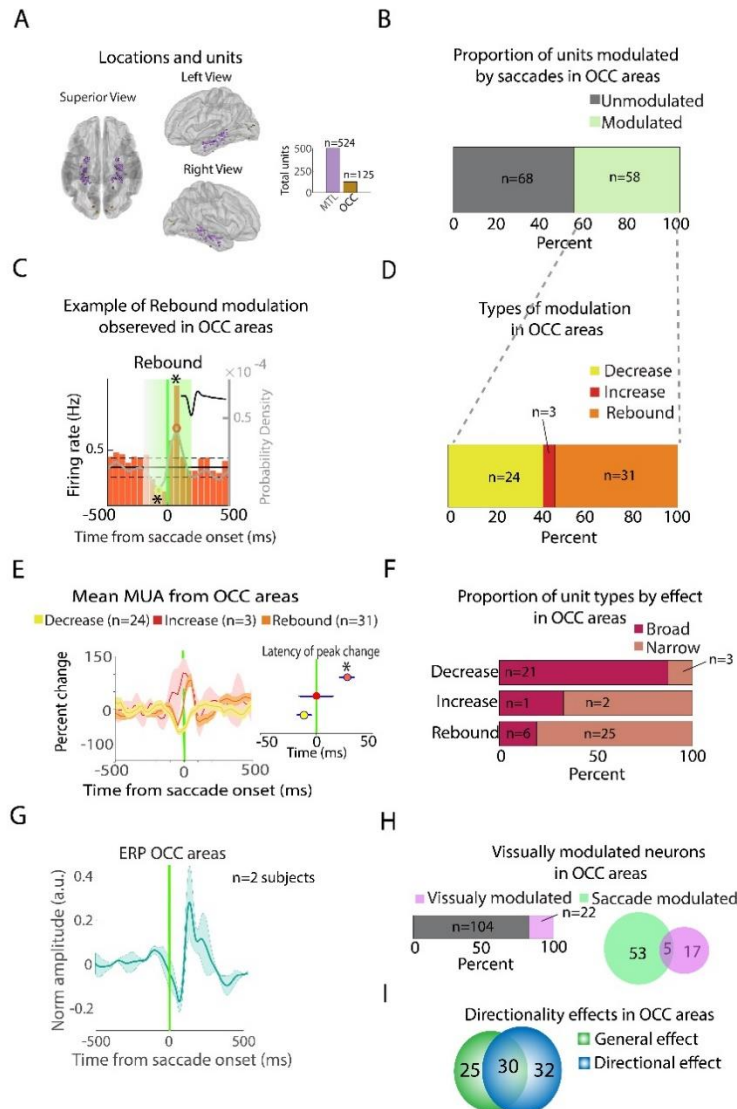


Figure S8.8 | Modulatory effects in Occipital areas: A) Electrode locations in occipital areas from 2 patients. Insert: Unit count in the OCC areas compared to the MTL areas; B) Distribution of units modulated by saccades; C) Firing rate histogram of exemplary unit presenting a Rebound Type of modulation observed only in OCC areas (mean waveform of the unit in top right insert). Asterisks represent significant decreases (yellow circle) or increases (red circle) within the perisaccadic period (green box). Gray superimposed line

indicates probability density (right y-axis) for visualization purposes. D) Distribution of the different types of modulation observed as explained in the methods section. E) Mean MUA from modulated units in the OCC. Insert shows the latency of the peak change in firing rate from the MUA traces; F) Proportion of 'broad' and 'narrow' spiking separated by the effect in firing rate in the perisaccadic interval; G) Mean ERP of electrodes in the MTL aligned to saccade onset; H) Left: the proportion of visually modulated neurons in the OCC; Right: Venn diagrams show the proportion of units visually or saccade modulated. Note that there is a significant overlap of units responding to both events in the OCC; I) The majority of saccade modulated neurons also present a directional modulation. MTL- Mesial temporal lobe; OCC- Occipital.

8.2.2 Figure S2

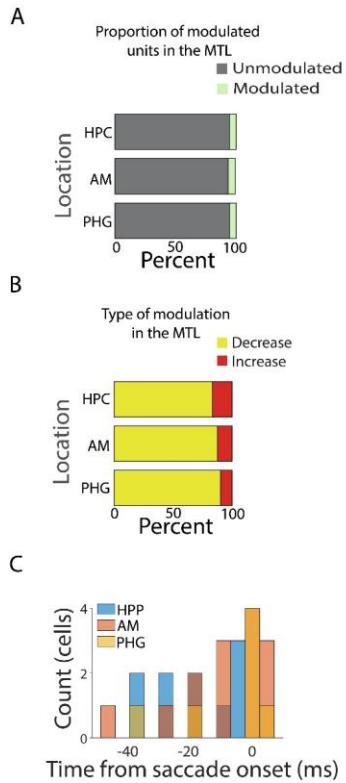


Figure S8.9] Modulatory effects are similar within different areas of the MTL: A) Proportion of cells modulated in the perisaccadic interval separated by the different anatomical locations; B) Types of modulation observed in the MTL separated by the different anatomical locations. C) Latencies of units modulated (decreases only) by saccade by MTL location. Note strong modulation within the saccadic onset.

8.2.3 Figure S3

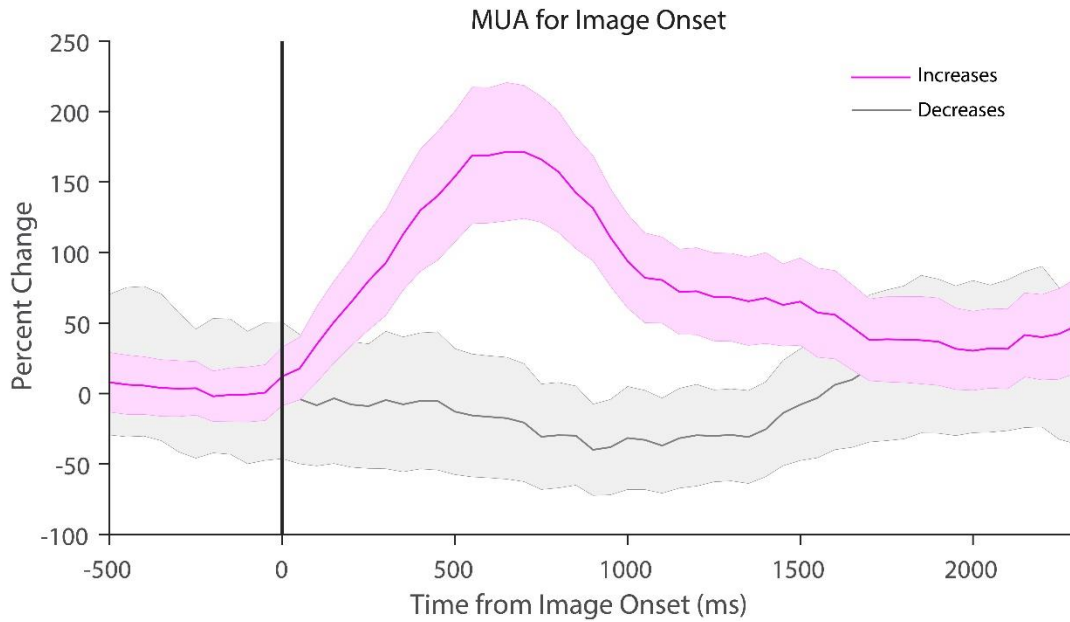


Figure S8.10| Multiple Unit Activity (MUA) of units modulated by image onset: Modulation was characterized by significant increases in firing rate starting around 300ms and returning to average levels after approximately 1300ms.

8.2.4 Figure S4

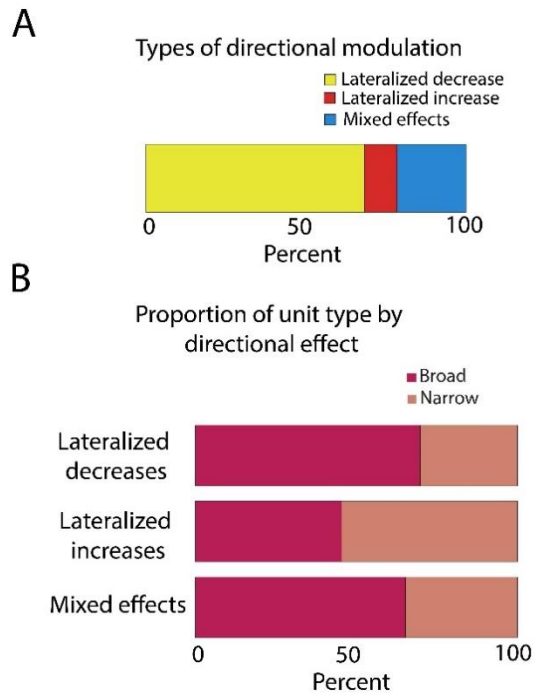


Figure S8.11| Characteristics of directional modulation in the MTL: A) Distribution of the different types of directional effects observed in the MTL; B) Proportion of 'broad' and 'narrow' spiking separated by the directional effect observed in the MTL.