UNIVERSITY OF CALIFORNIA,
IRVINE

The precision of memory for time in the human brain

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Biological Sciences

by

Maria E. Montchal

Dissertation Committee:
Professor Michael Yassa, Chair
Associate Professor Norbert Fortin
Professor Craig Stark

2019

DEDICATION

To Messrs. Pizzolo, Peluso, Nicholson, Brooks and Mmes. Valitzki, Dooley, and Montagna.

To Professors Lakin, Dolan, Abramowitz, and Knowles.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGMENTS

I thank my committee chair and advisor, Dr. Mike Yassa, for his mentorship, creativity, optimism, and support throughout this process. I deeply appreciate your willingness to listen to new ideas, even when they contradict your own. Most of all, your unrelenting support has been incredibly valuable throughout my time in your lab. Throughout our many disagreements, issues with data analysis, exploring career options, I have always felt that we are on the same team, and that has helped me to deal with the many challenges of graduate school and science.

I thank past and present committee members, Drs. Craig Stark, Norbert Fortin, Raju Metherate, and Elizabeth Loftus. I appreciate your feedback, and it has helped me move forward on my projects and craft a plan that led me to this point. I additionally thank Dr. Craig Stark for fielding countless questions on computing and for sharing some of your extensive knowledge on data analysis (particularly AFNI commands).

I thank past and present members of the Yassa Lab for their encouragement and for supporting me by being so very weird yourselves. I thank Amanda Chun, Jessica Noche, Stephanie Doering, Rachon Sweiss, Martina Hollearn, Edge Yu, Kierstin Livermore, and Matt Tsai for assisting with data collection. I thank Eva Morozko, Natalie DiProspero, and Joren Adams for bonding with me over cats and for taking such good care of Nixon when I was gone. I also appreciate your friendship. I thank Zachariah Reagh for mentorship and senior-grad-student advice that was always on point. I thank Liz Murray for understanding what it is like to be a native east coast-er in Irvine, for sharing cat mom tips, and for being willing to get food with me when it was needed the most. I thank Joren Adams, Liv McMillan, and Anna Smith for sharing their office couch in various locations. It has served as a refuge for quiet writing that has been much appreciated. I thank Miranda Chappel-Farley for having an adorable fluffy-tailed orange cat and for never dropping me while belaying me on the rock wall. I thank Myra Larson for always having the answer, for your friendship, and for your precious doggos. I thank Manuella Yassa for being an amazing leader and endlessly supportive of all my endeavors. I thank John Janecek for coding what would have taken me hours in mere minutes. I thank the other members of the Yassa Lab: Luis Colon-Perez, Caroline Chwiesko, Sandra Gattas, Steven Granger, Logan Harriger, Rebecca Stevenson, Jessica Yaros, and our past and present research assistants for their contributions to the lab.

I thank members of the Rep Max Performance weightlifting gym for being an endless source of positivity and strength, especially Jeff Rother, Alana Hodge, Jerry Sanchez, Sussie Gil, Yen Nguyen, Beatriz Galsim, Kelly Chan, Ana Zelaya, and Brooke Valdez. Training with you all has shown me the importance of having fun, mental strength, and the power of positivity (and also the negative consequences of pessimism). I have thoroughly enjoyed putting barbells over my head with each and every one of you.

I thank Eva Morozko, Meaghan Hearn, and Teddy and Rosie for their friendship and knowledge of Taylor Ham. I thank Freddie Marquez, Josh Crapser, Isabella Sanchez, Elena Dominguez, and even Miguel Arreola for the food, drinks, and important conversation. I thank Sussie Gil for being my chosen family and always supporting and feeding me. I thank Nixon Montchal for helping me cope with life's stresses. I thank Mike Heumann for unwavering support, excessive science knowledge, and adventures.

Financial support for the work described in this dissertation was provided by US NIH grants P50AG05146, R01MH1023921, and R01AG053555 (PI: M.A.Y.), and Training Grant T32DC010775 (to M.E.M., PI: Metherate). I also thank the friends of the CNLM who have contributed to the Renée Harwick Advanced Graduate Student Award, Roger W. Russell Award in the Neurobiology of Learning and Memory, and the John W. Haycock Memorial Graduate Student Travel Award for supporting my research.

CURRICULUM VITAE

Maria Montchal

Academic history

2014-2019	**UC Irvine** PhD in Biological Sciences
2017	MS in Biological Sciences
2006-2010	**Drew University** B.A. in Psychology and French, Minor in Writing

Honors and Awards

2019	Renée Harwick Advanced Graduate Student Award
2018	Roger W. Russell Award in the Neurobiology of Learning and Memory
2017	John W. Haycock Memorial Graduate Student Travel Award
2015-17	T32 Center for Hearing Research Training Grant
2014-15	UC Irvine- Biological Sciences Graduate Fellowship Award
2014-15	UC Irvine Graduate Dean Recruitment Fellowship Award
2014	NSF Graduate Research Fellowship Program Honorable Mention

Publications

Montchal, M.E., Reagh, Z.M. & Yassa, M.A. (2019). Precise temporal memories are supported by the lateral entorhinal cortex in humans. *Nature Neuroscience*, Epub ahead of print. doi: 10.1038/s41593-018-0303-1.

Ritchey, M., **Montchal, M.E.**, Yonelinas, A.P., & Ranganath, C. (2015). Delay-dependent contributions of medial temporal lobe regions to episodic memory retrieval. *Elife,* 13(4).

Wang W.C., **Montchal M.E.**, Yonelinas A.P., Ragland J.D. (2014) Hippocampal and parahippocampal cortex volume predicts recollection in schizophrenia. *Schizophr Res*, 157, 319-20.

Select Presentations

Montchal, M.E. and Yassa, M.A. (2018 November). Effect of repeated immediate reactivation on memory performance. Poster presented at the Society for Neuroscience Annual Meeting.

Montchal, M.E., Reagh, Z.M, & Yassa, M.A. (2018 January). Object but not spatial network engagement for temporally precise memory judgments. Talk presented at the Park City Winter Conference Annual Meeting.

Reagh, Z., Mattfeld, M., Allen, T., **Montchal, M.E**., & Yassa, M.A. (2017, March). Structural and functional evidence for thalamic nucleus reuniens in the human brain. Presented at the Cognitive Neuroscience Society Annual Meeting.

Montchal, M.E. and Yassa, M.A. (2016, November). Hippocampal-cortical networks for temporal memory precision. Poster presented at the Society for Neuroscience Annual Meeting.

Montchal, M.E. and Yassa, M.A. (2016, March). Precise and less precise temporal memory judgments recruit different hippocampal-cortical functional networks. Presented at the Cognitive Neuroscience Society Annual Meeting.

Roberts, B., Wang, S-F., **Montchal, M.E.**, Wade, A., Bouffard, N., Ragland, D., Carter, C., & Ranganath, C. (2016, November). Effects of transcranial direct current stimulation (tDCS) on neural oscillations during episodic memory encoding and retrieval. Presented at the Society for Neuroscience Annual Meeting.

Montchal, M.E. & Yassa, M.A. (2016, April). Precise and less precise temporal memory judgments recruit different hippocampal-cortical functional networks. Presented at the Cognitive Neuroscience Society Annual Meeting.

Roberts, B., Wang, S., **Montchal, M.E**., Wancewicz, B., Carter, C., & Ranganath, C. (2014, November) Combined working memory exercise and prefrontal transcranial direct current stimulation influences cognitive control. Presented at the Society for Neuroscience Annual Meeting.

Academic Service

- Independent ad hoc reviewer for *Proceedings of the National Academy of Sciences of the United States of America* (November 2018-present)
- Ad hoc reviewer for *Brain and Cognition, Neuropsychologia, Hippocampus, The Journal of Neuroscience,* and *Cerebral Cortex* (assisted Dr. Michael Yassa, June 2015-present)

Professional Memberships and Affiliations

- Society for Neuroscience (2013-present)
- Cognitive Neuroscience Society (2013-present)
- Hippocampal Subfield Segmentation Summit (2013-present)

Science Policy/Advocacy

California Council on Science & Technology
Science Translator Showcase Participant **January-February 2019**
Attended a series of webinars addressing how to effectively communicate with legislators. The program culminated in an in-person session where I discussed my research with legislators in Sacramento.

Alzheimer's Association Advocate **May 2018-present**
Attended State Advocacy Day in February 2019 in Sacramento, CA and attended Forum Day in Washington, D.C. in June 2018, where I discussed the importance of funding Alzheimer's research. Volunteered in the 'Ask a Researcher' booth at the 2018 Walk to End Alzheimer's in Irvine and discussed research and brain health.

AAAS CASE on the Road Attendee **October 2018**
Learned about the federal government and effective advocacy. Attended sessions on state and local advocacy, how to effectively communicate a story to policymakers, and science policy fellowships.

Judicial Seminar on Emerging Issues in Neuroscience Guest **October 2018**
Informally discussed the brain and memory with a group of federal judges. Invited by speaker Dr. Craig Stark due to my expressed interest in science communication and policy.

Leadership

Graduate Representative **September 2016-2018**

Served as a liaison between graduate students and faculty; resolved conflicts, attended faculty meetings, and organized events for graduate students within the department.

Mentoring Workshops **October 2014-present**

- UCI Peer-run Mentoring Workshop- Learned about common problems in mentor-mentee relationships and how to navigate them. Created a mentoring philosophy to share with mentees to communicate expectations (April-June, 2016).
- UC Irvine Mentoring Excellence Program- Learned strategies to deal with conflicts, communicate effectively, and foster productive habits (July-August, 2015).
- UC Irvine Biological Sciences Mentor Program- Met with and advised three students interested in neuroscience throughout their undergraduate and post-graduate careers (October 2014-present).

Science Communication

ComSciCon Flagship Workshop **July 2019**

Attended the Flagship Workshop in a competitive pool of applicants. Wrote, workshopped, and complete an original piece for an audience of non-scientists.

NeuroCrew Writer (paid) **April 2019-present**

Writing blog posts and writing/editing neuroscience pieces

Loh Down on Science Script Writer (paid) **May 2019-present**

Writing 10 scripts, to be read on the *Loh Down on Science* radio show.

Communications Committee Chair, CNLM Ambassadors Program **September 2018-present**

Started series of 'scientist spotlight' interviews to showcase scientists involved in the Center for the Neurobiology of Learning and Memory (CNLM). Facilitated the writing of other blog pieces and newsletter materials summarizing CNLM Ambassador events, experiences, and new research.

Select Outreach and Education

- **Brain Explorer Academy Mentor-** Mentored 2nd-7th grade students as they gave feedback on a journal article written for children their age (January-April 2018).
- **Tech Trek Presenter-** Organized, created, and presented a lecture about the brain and fMRI for high school girls to encourage them to think about themselves as future scientists and engineers (July 2017 and 2018).
- **Invited Speaker at Drew University-** Discussed my path to becoming a PhD student, how undergraduates can become involved in research, and described a day in the life of a typical PhD student. (October 2017)
- **Ask a Scientist Night Volunteer Scientist-** Advised 6-8th graders on science fair projects, aiming to ensure that they had clear hypotheses and sufficient controls in their experiments and helped to foster scientific thinking and interest in science. (August-September 2017)
- **Brain Awareness Day Volunteer-** Presented information about neuroscience, answered questions, and helped middle schoolers at Isaac Sowers Middle School to learn about, handle, and examine preserved brains. (March 2017)

ABSTRACT OF THE DISSERTATION

The precision of memory for time in the human brain

By

Maria E. Montchal

Doctor of Philosophy in Biological Sciences

University of California, Irvine, 2019

Professor Michael A. Yassa, Chair

Many studies have provided evidence that the medial temporal lobes of the brain are involved in memory for everyday life experiences (episodic memory). Episodic memory has several components: the event itself (*what*), *where* the event took place, and *when* the event took place. The goal of this dissertation was to understand how the brain supports memory for *when* events occur (temporal memory). We showed participants an episode of *Curb Your Enthusiasm* inside of the MRI scanner, to monitor task-related changes in relevant brain regions. Then, we tested participants' memory for when events in the episode occurred. We found that a network of brain regions, including the hippocampus, lateral entorhinal cortex (LEC), and perirhinal cortex (PRC) were preferentially activated when participants were closest to the correct answer. This suggests that memory for time may have different neurobiological correlates than memory for spatial information. Cortical regions, such as medial prefrontal cortex, angular gyrus, and posterior cingulate cortex were also activated when participants responded most precisely, indicating that they may also support temporal memory

precision. We found no evidence that scene changes (event boundaries) had an effect on temporal memory performance in this task. A cluster in the superior temporal gyrus was preferentially activated at event boundaries while participants watched the episode, which could reflect changes occurring at boundaries, music during the episode, or both. We also tested older adults on this task and their performance correlated with a neuropsychological test of memory involving remembering words over a delay. Future studies of memory for time involving more naturalistic stimuli will provide additional information on brain-behavior relationships critical for remembering when events occurred.

INTRODUCTION

This dissertation focuses on one critical component of episodic memory: memory for *when*. Memories are organized in time, but we cannot always recall when a specific event happened, even if we can remember the event itself. Important work over the last several decades has provided compelling evidence that certain brain regions, such as the hippocampus, are part of a network that encodes and retrieves this timing information (Hsieh, Gruber, Jenkins, & Ranganath, 2014; MacDonald, Carrow, Place, & Eichenbaum, 2013; Tubridy & Davachi, 2011b). However, it remains unclear exactly how the brain accomplishes this and what other regions may be involved.

Aside from bringing the field closer to understanding the brain networks that support memory for timing information, this work also has implications for neurodegenerative disorders, such as Alzheimer's disease. Understanding how the healthy brain works can help us understand what goes wrong with the brain. Imagine your brain as a car. If you had motor oil sludge that was making your car stall, simply replacing the oil might not fix the problem. You would need to know how the whole car works to identify the source of the issue. Learning about the brain networks involved in memory for time gives us valuable information about a part of the car that is just beginning to be understood.

Aim 1: Use a naturalistic memory task to characterize networks that support memory for precisely when events occurred.

The current study utilized naturalistic stimuli (a television show) and required participants to make temporal memory judgments. Participants saw still-frames from the

television show, one at a time, and had to place each one on a timeline to indicate when it occurred.

Most investigations of temporal memory use a binary measure of accuracy (correct or incorrect). This may obscure some information, since people can be seconds, minutes, or even days from the correct answer to when an event occurred. It is possible that different brain regions support precise temporal memory vs. more coarse-grained temporal memory (being within a few minutes of the correct answer). Since episodic memories are so vivid and detailed, certain circuits may be preferentially involved in temporal memory for these events, as opposed to those in a typical laboratory experiment involving viewing objects on a computer screen. Specifically, the hippocampus and prefrontal cortex have been implicated in temporal memory, and we sought to test whether these regions would also support memory for time in a more naturalistic task.

This project identified brain networks that preferentially support the most precise temporal memory judgments. Several brain regions that were more active for the most precise trials fit well with previous literature on memory for time, such as the hippocampus (Hsieh et al., 2014; Jenkins & Ranganath, 2010; Ranganath & Hsieh, 2016; Salz et al., 2016). However, finding the same pattern in PRC and LEC but not PHC and MEC was unexpected and may reflect a role for the LEC/PRC network in memory for time (Tsao et al., 2018). We found the same pattern in cortical regions

including angular gyrus and posterior cingulate cortex, regions that have been previously implicated in memory for details.

Aim 2: Assess the effect of event boundaries on temporal memory performance and BOLD fMRI activity.

Prior work on event segmentation suggests that chunking experiences into events improves memory (Flores, Bailey, Eisenberg, & Zacks, 2017; Heusser, Ezzyat, Schiff, & Davachi, 2018; Newtson & Engquist, 1976). However, these studies have not tested effects on memory precision related to timing information specifically, and instead have generally focused on recognition memory or contextual memory for a feature other than time. To fill this gap in the literature, we tested whether the closest one third of trials to event boundaries (defined here as scene changes) were associated with increased temporal precision performance. We found no evidence that proximity to an event boundary affects temporal memory precision. We additionally tested whether brain regions increased their activity at event boundaries, as previously reported in the hippocampus (Ben-Yakov & Henson, 2018) and superior temporal gyrus (Speer, Zacks, & Reynolds, 2007). We found significant clusters in the superior temporal gyrus, consistent with previous findings (but could be related to music played during the episode), but no significant clusters in the hippocamus.

Aim 3: Test older adults on this same paradigm to determine whether the task is sensitive to brain changes in normal aging.

Older adults perform worse than young adults on memory tests (Davis et al., 2013; Dumas & Hartman, 2003; Harada, Love, & Triebel, 2013), including those testing memory for time (Fabiani & Friedman, 1997; Pirogovsky et al., 2013; Seewald et al., 2017). Additionally, recent work found alterations in DGCA3/LEC activity in older adults with decreased object memory performance (Reagh et al., 2018). This is particularly of interest because these regions were found to be preferentially active during the most precise temporal memory trials in young adults in Aim 1. Surprisingly, we found that older adults performed comparably to young adults on this test of memory for time. We speculate that this could be due to allowing older adults more time to respond or our lower sample size. We also found a correlation between task performance and RAVLT-Delay scores in older adults, indicating that our task may tax mnemonic processes related to standardized neuropsychological tests. Future work should investigate whether cortical thickness in medial temporal lobe subregions is related to task performance.

CHAPTER 1: Background and Significance

Cognitive Neuroscience of Memory

Since Aristotle, memory has been described as a core component of the human experience. Early philosophers and scientists began to separate memory into different types. One major distinction is between declarative and non-declarative memory. This dissertation focuses on one sub-type of declarative memory called episodic memory. Episodic memory is memory for events in our lives. Patients with brain lesions have provided evidence that the hippocampus is necessary for forming episodic memories and retrieving recent episodic memories (Scoville & Milner, 1957). Related work has identified the existence of multiple memory systems that support episodic and declarative memory. For example, eight amnestic patients were able to learn the mirror drawing task as well as controls (Cohen & Squire, 1980). This finding has been replicated in non-human primates and rats with hippocampal lesions (Gould et al., 2002; Zola-Morgan & Squire, 1984).

Episodic memory contains three main components: what, where, and when. Whether non-human animals are capable of episodic memory has been a controversial topic. Non-human animals have different motivations, capabilities, and behavioral outputs than humans, which makes paradigm selection challenging. One team found that scrub jay birds were able to remember and locate food that had been cached recently, using

one type of food that rots quickly and one that stays fresh for over 100 hours. This required scrub jays to recall the type of food (*what*), *when* they had cached it, and *where* they had cached it (Clayton & Dickinson, 1998). The scrub jays were able to keep track of all three components of episodic memory, to retrieve fresh food they had hidden. This provides evidence that non-human animals with differently structured brains can exhibit episodic memory. It also gives important insight into the purpose of memory throughout evolution. From scrub jays to humans, episodic memory helps us navigate through the world and learn from our experiences.

Medial Temporal Lobe Contributions

Structural and functional organization of the medial temporal lobes

How does the brain allow us to recall events that happened in our lives? Together, human and animal studies have added to our understanding of hippocampal function and anatomy. The study of one man named Henry Molaison provided critical insight into the function of the medial temporal lobes (MTL). Molaison had several MTL subregions removed in an effort to treat his epilepsy. After the surgery, he was unable to remember anything that happened more than a few minutes earlier (Milner, 1962). Since then, the field has learned more about how specific MTL subregions contribute to episodic memory.

The hippocampus in humans is an intricate structure with several subfields that differ in both anatomical connectivity and function. The hippocampus is thought to index memories, meaning that it can reactivate neurons from different brain regions, such as visual or auditory cortices, during recall (Teyler & Discenna, 1986). It is anatomically poised to serve as an index, since it receives input from much of the rest of the brain through the parahippocampal cortex (PHC), perirhinal cortex (PRC), and entorhinal cortex (ERC) (Wendy A. Suzuki, 1996; Witter et al., 2000).

The hippocampus also has unique anatomical features that likely shape its contribution to memory. There are two main paths through the hippocampus. In the trisynaptic path, neurons in layer II of the ERC activate the dentate gyrus (DG) subfield of the hippocampus. The DG then activates neurons in CA3. CA3 has recurrent collaterals, which synapse onto other neurons in CA3. Schaffer collaterals of CA3 activate neurons in CA1 (Andersen, Bliss, & Skrede, 1971). CA1 neurons, in turn, activate the hippocampal subiculum which connects to layers IV and V of the entorhinal cortex. The autoassociative structure of CA3 may contribute to its ability reactivate prior activity patterns based on partial inputs. The interconnected structure of CA3 recurrent collaterals allows for long-range associations to be formed between neurons (Rolls & Kesner, 2006). Then, when the system receives a partial input, it is better able to reactivate the whole memory. This hypothesis is supported by several rodent studies (A. E. Gold & Kesner, 2005; Vazdarjanova & Guzowski, 2004) but is more difficult to test in

humans, since CA3/DG are usually impossible to segment even in high resolution functional magnetic resonance imaging (fMRI).

In the monosynaptic pathway, layer III of the ERC can also directly activate CA1 and CA2 (Zemla, R. & Basu, 2016). **Figure 1** gives a simplified illustration of hippocampal connectivity. CA1 is in a unique position, since it receives processed mnemonic information from CA3 and less processed, more perceptual information from layer III of ERC. Based on this anatomical structure, CA1 may be poised to act as a comparator, detecting when predictions are violated (Kumaran & Maguire, 2009; Lisman & Grace, 2005).

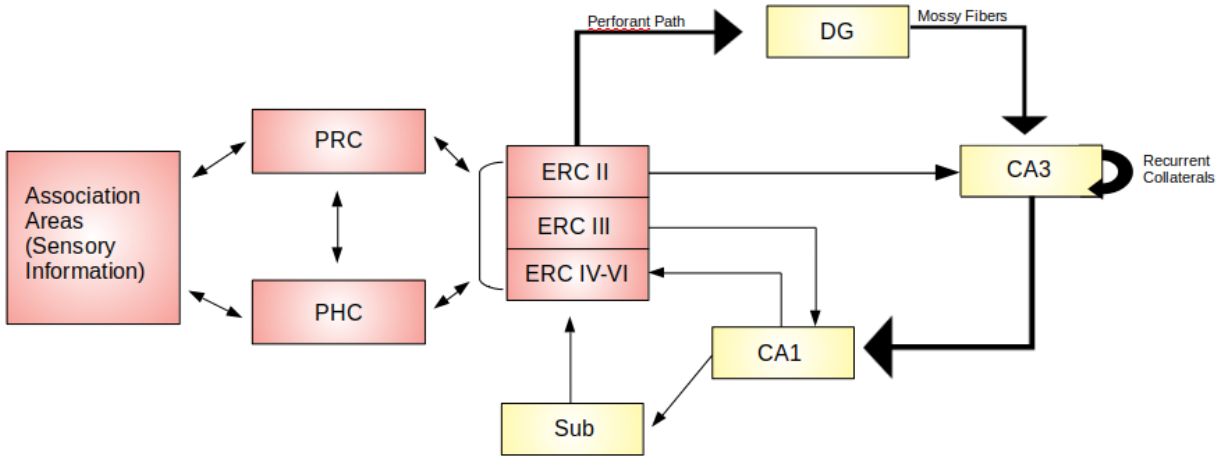


Figure 1: A simplified view of anatomical connectivity of relevant medial temporal lobe regions. Adapted from Wilson (2006).

Information enters the hippocampus through the ERC. The LEC and the medial entorhinal cortex (MEC) also have different anatomical connections which seem to be reflected in their function. The LEC is strongly connected to PRC, whereas MEC is strongly connected to PHC (Burwell & Amaral, 1998; Insausti, Herrero, & Witter, 1997). Grid cells have been identified in MEC (Brun et al., 2008; Diehl et al., 2017), whereas LEC neurons exhibit less spatial selectivity in their firing (Deshmukh & Knierim, 2011; Keene et al., 2016).

Information enters the ERC from perirhinal cortex (PRC) and parahippocampal cortex (PHC). These regions receive information primarily from visual cortex but also from other association areas, such as frontal, temporal, and parietal lobes (Aggleton & Brown, 1999; Lavenex & Amaral, 2000). PRC's main inputs come from the ventral visual processing stream, whereas PHC is connected to the dorsal visual stream (W A Suzuki & Amaral, 1994; Wendy A. Suzuki, 1996). This pattern of connectivity seems to be reflected in their function, with studies finding PHC being involved in spatial memory (Epstein, Parker, & Feiler, 2007; Krumm et al., 2016) and PRC in object memory (Aggleton, Kyd, & Bilkey, 2004; Ramos, 2002; W. a Suzuki, Zola-Morgan, Squire, & Amaral, 1993).

More specifically, PHC is thought to support memory for "context" which is often nebulously defined and can include an encoding question, a background image, or a

spatial location (Stark, Reagh, Yassa, & Stark, 2018). It seems likely that the spatial information that comes to PHC through the dorsal visual stream and its many connections with other brain regions, such as retrosplenial cortex, the hippocampus, and prefrontal cortex (Aminoff, Kveraga, & Bar, 2013) play a key role in organizing spatial information in memory. Rodent studies have found that postrhinal cortex lesions (the rodent homolog to PHC) lesions result in impaired spatial memory (Bussey, Duck, Muir, & Aggleton, 2000; Liu & Bilkey, 2002). A recent study found that human patients with PHC damage were impaired on a spatial memory task (Bohbot et al., 2015). Patients with hippocampal lesions performed just as well as controls on this task, suggesting that the PHC makes additional contributions to spatial memory, beyond simply being part of the extended hippocampal circuit.

PRC, on the other hand, seems to be involved in memory for and visual processing of objects (Buckley & Gaffan, 2000; Buffalo et al., 1999; Keene et al., 2016). Its anatomical connectivity to inferotemporal visual areas puts the PRC in a prime location to process object information (Burwell & Amaral, 1998). In humans, PRC has been found to be associated with recognition and object memory, with this region playing less of a role in memory for “context” involving spatial information (Hasselmo, 2005; Mundy, Downing, Dwyer, Honey, & Graham, 2013; Staresina, Duncan, & Davachi, 2011).

Understanding these anatomical connections is critical, since it is extremely unlikely that one brain region is responsible for any given mnemonic function. There is evidence that a network of medial temporal regions including, but not limited to the hippocampus (Doron & Goshen, 2017; R. Kesner, Gilbert, & Barua, 2002; Lehn et al., 2009; MacDonald, Lepage, Eden, & Eichenbaum, 2011), entorhinal cortex (Lositsky, Chen, Toker, Honey, Poppenk, et al., 2016; Naya & Suzuki, 2011), prefrontal cortex (Devito & Eichenbaum, 2011), and likely other regions all contribute to temporal memory. A combination of anatomical, neuroimaging, lesion, and behavioral data will elucidate what regions may be involved in a temporal memory network.

Memory for Timing Information

Memories are organized in time, which allows us to make sense of and learn from our experiences. Richard Semon discussed the "body watch" and the integration of time into memory in the early 20th century (Semon, 1921). How does the brain allow us to recall when events in our lives occurred? Important contributions have been made to answering this question, which are described in the following sections, but large gaps in knowledge remain in this field.

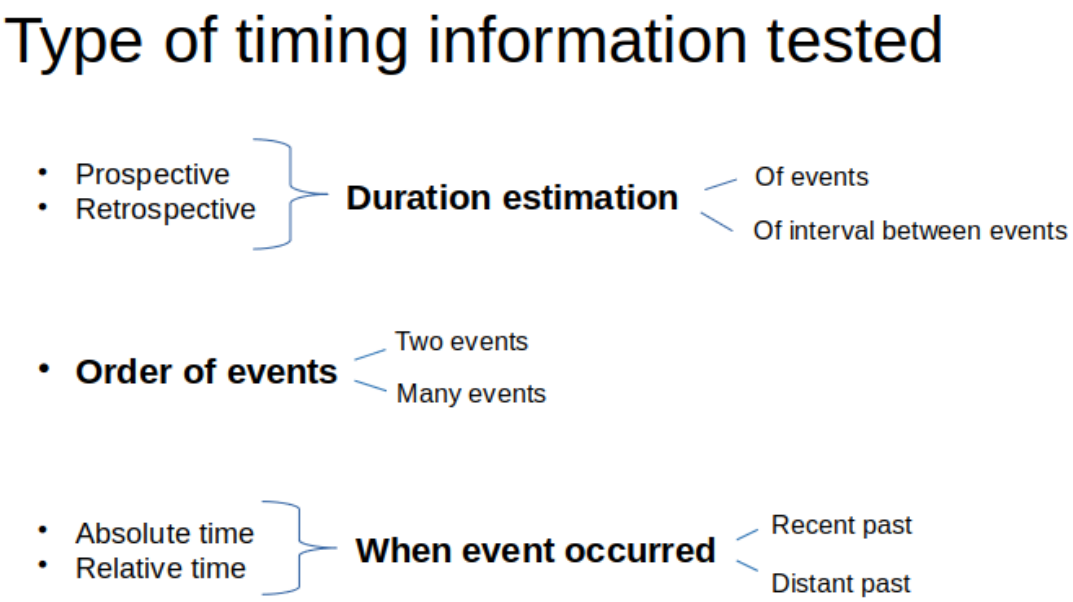


Figure 2: Important parameters to consider when conducting or interpreting studies of temporal memory.

When conducting or interpreting research about memory for timing information, it is important to consider the *type* of timing information that is being tested (**Figure 2**). There are likely distinct neural mechanisms underlying cognition and memory for each type of timing information. For example, duration estimation likely involves more intrinsic timing mechanisms in cortical-striatal circuits (Buhusi & Meck, 2005), whereas determining the order of events likely has much more of a mnemonic component and may involve more recruitment of hippocampal and medial temporal lobe networks.

This dissertation focuses on memory for when events occurred. Memory for when events occurred was tested in absolute time (participants had to place each on a

timeline, one at a time, from the beginning of the episode to the end), but they may have also used relative time to make these judgments (thinking about whether other scenes occurred before or after the current still-frame). The events were all in the recent past, since the ~30-minute episode began about an hour before event timing was tested.

It is also important to note that certain experimental parameters likely also influence the networks supporting each type of timing information in the brain. For example, there is evidence that memory for dynamic real-life experiences have different neural correlates than memory for static images (Cabeza et al., 2004), which likely extends to other types of memory such as memory for time. Other potentially important variables include whether information is learned in one-shot vs. studied, events that logically flow vs. have an unexpected order, the duration of events, and the duration *between* events that are tested.

There is considerable evidence suggesting that the hippocampus is involved in memory for time. However, exactly how the factors discussed above or the types of temporal memory have shared or divergent neural correlates remains unclear. As more studies contribute findings on memory for time, researchers will be better able to integrate findings from other work on specific aspects of temporal memory.

Computational Models

There is no consensus on exactly how timing information is incorporated into memory. Two models have been proposed: 1) hippocampal neurons fire to create a slowly evolving temporal context, which is integrated into memories or 2) sequential events are linked to one another through an associative chaining mechanism (Jensen & Lisman, 2005).

Both models have some supporting evidence but leave other phenomena unexplained. For example, the associative chaining model cannot completely explain our ability to disambiguate partially overlapping sequences (e.g. separating where your car is parked today vs. two days ago) (Eichenbaum, 2014). According to this model, each event can only ever be associated with the event immediately preceding and following it. Temporal context models avoid this issue, since even events that are extremely close in time will be associated with slightly different hippocampal firing patterns. Consistent with the temporal context model, there is evidence that the hippocampus produces an evolving pattern of activity that becomes less similar over time (Mankin et al., 2012; Manns, Howard, & Eichenbaum, 2008). In humans, this has been shown to interact with memory retrieval. When people were repeatedly shown different video clips, a repeated viewing elicited a pattern of activity similar to the initial viewing of the scene (Howard, Viskontas, Shankar, & Fried, 2012). This work brings the field one step closer to understanding the neural basis of mental time travel. Further research is needed to

understand exactly how the hippocampus and other brain regions work together to integrate time into memory. The answer may lie in some mix of the two popular models, or something as yet undiscovered.

Memory for Order

Rats can correctly identify which odor came first in a sequence, but rats with hippocampal lesions were impaired on this task, except for trials with the largest temporal lag between odors. It is important to note that these rats were not impaired at recognizing familiar odors (Kesner, Gilbert, & Barua, 2002). Another study found that rats with hippocampal or medial prefrontal damage had impaired memory for the order of odors (Devito & Eichenbaum, 2011).

In humans, hippocampal lesions are associated with deficits in remembering the order of words (Mayes et al., 2001). Patients with hippocampal lesions were not impaired at recognizing words they had previously seen, suggesting that this deficit is specific to memory for order. Another study found similar results with objects picked up during navigation. A patient with a hippocampal lesion could not recall the order of objects but could recognize familiar objects (Spiers, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2001).

Several studies have shown hippocampal activation in healthy young adults remembering object order (Ekstrom & Bookheimer, 2007; Lehn et al., 2009). Other

studies have shown hippocampal activity at encoding was related to later success at recalling temporal information (Jenkins & Ranganath, 2010; Staresina, 2006; Tubridy & Davachi, 2011a).

The hippocampus does not act alone in supporting memory for time. Patients with prefrontal lesions were found to have impaired memory for temporal order, but intact recognition memory (Shimamura, Janowsky, & Squire, 1990). Similarly, rats with prefrontal damage showed impaired temporal order memory but were no different than controls on recognition (Devito & Eichenbaum, 2011), and inactivation of medial prefrontal cortex (mPFC) impaired time interval discrimination in rats without altering response bias or latency (Kim, 2009).

Time Cells

Our understanding of how time is integrated into memory was changed by the discovery of “time cells” in the hippocampus. These are cells that have a preferred time to fire during inter-trial intervals in a plus-maze task (MacDonald et al., 2011).

There is evidence that the very same cells can have reliable firing patterns for both space and time (Kraus, Robinson, White, Eichenbaum, & Hasselmo, 2013; MacDonald et al., 2011). Time cells can “retime” just as place cells “remap” when parameters they encode are changed (MacDonald et al., 2011). Even within the hippocampus, space is

represented differently in different anterior-posterior (ventral-dorsal in rodents) locations, with fewer place cells and larger place fields in the dorsal (anterior) hippocampus (Jung, Wiener, & McNaughton, 1994). Similarly, time cells have different durations of activity, or "time fields," (MacDonald et al., 2011) although this does not seem to be dependent upon the cell's location within the hippocampus.

Timing Information: Origins and Integration into Memory

Where do time cells get their timing information? Time perception involves information from all senses and can be affected by attention, disease, and arousal (El Haj & Kapogiannis, 2016; Fontes et al., 2016). It has been especially challenging to determine how the brain supports timing for various interval durations, since these durations vary from milliseconds to hours or more. A review by Buhusi and Meck (2005) suggest that timing on different timescales is supported by the regions depicted in **Table 1**.

Table 1: Brain regions involved in tracking timing information for different durations. Adapted rom Buhusi and Meck (2005).

Interval duration	Region(s) involved	Uses
Hours	Suprachiasmatic nucleus	Regulation of biological rhythms
Seconds to minutes	Cortico-striatal circuits	Decision making, conscious time estimation
Milliseconds	Cerebellum	Speech, motor control

Once we fully understand how the brain executes interval timing, we still need to explain exactly how that information is communicated to memory systems. There is evidence that the suprachiasmatic nucleus sends information about time of day to the hippocampus (see Hut & Van der Zee, 2011 for review). The basal forebrain provides cholinergic inputs to prefrontal cortex (Mesulam, Mufson, Wainer, & Levey, 1983), and pharmacological manipulation acetylcholine can affect estimates of duration (Matthews & Meck, 2016). Further research is needed to determine exactly how clocking mechanisms affect temporal memory encoding and retrieval (and perhaps vice versa). The present work focuses on memory systems only after they have received and integrated this information.

There is evidence that the hippocampus also keeps track of the passage of time. Researchers found that the hippocampus was required for rats to discriminate between small differences in elapsed time, specifically over a timescale of minutes (Jacobs, Allen, Nguyen, & Fortin, 2013). Similarly, human patients with hippocampal damage were impaired at making duration estimations for long (4 minute) durations (Palombo, Keane, & Verfaellie, 2016). Studies have shown that patterns of hippocampal ensembles evolve gradually over time, even when controlling for potential confounds like spatial context (Mankin et al., 2012; Manns et al., 2008). However, one fMRI study found that hippocampal BOLD fMRI patterns distinguished between overlapping

sequences only for learned sequences (Hsieh et al., 2014), which would argue against the existence of an automatic clocking mechanism in the hippocampus.

There is also evidence that this temporal information can be bound to other aspects of an experience. Rats used odor and location information to remember the order of odors in a sequence. Rats with hippocampal damage were impaired even though they showed intact memory for odors and locations alone (Ergorul & Eichenbaum, 2004). Patterns of firing reflected both temporal and task (right or left turn) information. This was true despite the fact that spatial information was held relatively constant, since rats were on a running wheel (Pastalkova, E., Itskov, V., Amarasingham, A., and Buzsáki, 2008). In humans, hippocampal fMRI activity patterns were found to carry conjunctive information about duration and objects (Thavabalasingam, O'Neil, Tay, Nestor, & Lee, 2019). Hippocampal ensembles that predicted performance represented both temporal and odor information (Manns et al., 2008). This evidence suggests the hippocampus encodes several types of contextual information, depending on the task.

Importantly, timing information in the brain has also been related to memory accuracy. In rodents, patterns of activity in the hippocampus were related to successful performance on an object order task (Manns et al., 2008). In one study, gradually evolving hippocampal patterns developed as humans repeatedly watched the same film clips. The degree to which these patterns were correlated predicted later memory

performance (Paz et al., 2010). Several studies have found that success at recalling temporal information was predicted by hippocampal activity (Jenkins & Ranganath, 2010; Staresina, 2006; Tubridy & Davachi, 2011b).

The brain networks that support memory for time are not yet fully understood. The literature indicates that the hippocampus and prefrontal cortex are likely necessary for making memory judgements involving temporal order. There is more limited evidence that the entorhinal cortex is involved in memory for time. However, how these regions work together to support memory for timing information of real-life experiences on different timescales remains unclear. The goal of the current work is to contribute to this critical question.

The Role of LEC

Despite evidence that the hippocampus codes for and integrates some aspects of timing information into memory, it remains unclear exactly how this occurs on timescales from milliseconds to hours. Interestingly, recent work has focused on lateral entorhinal cortex (LEC) because it is a major hippocampal input and is relatively understudied.

Recently, researchers found that individual LEC neurons and ensembles both encoded temporal information (**Figure 3**) (Tsao, A., Sugar, J., Lu, L., Wang, C., Knierim, J.J.,

Moser, M., and Moser, 2018). LEC activity reflected the passage of time from the scale of seconds to hours. LEC encoded time both when animals were engaged in a task and when they were free to explore, though activity during the task was encoded with respect to temporal landmarks (Tsao, A., Sugar, J., Lu, L., Wang, C., Knierim, J.J., Moser, M., and Moser, 2018).

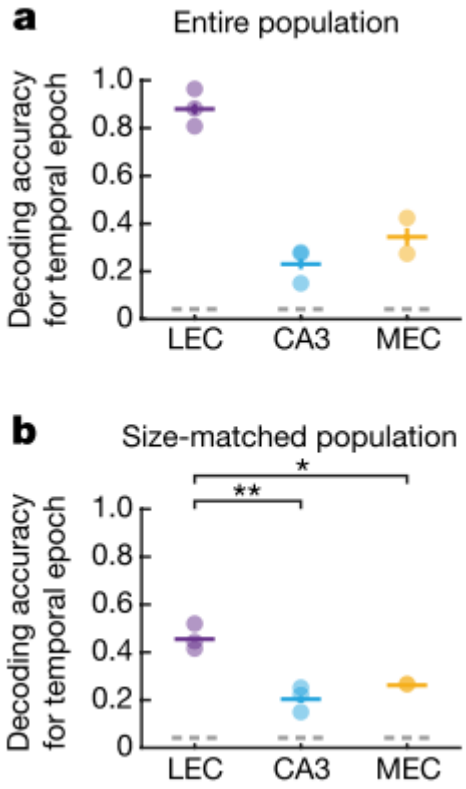


Figure 3: Decoding accuracy for LEC, CA3, and MEC for a) the entire population and b) a size-matched population of neurons, from Tsao, Sugar, Lu, et al. (2018).

The authors propose that LEC activity may contribute to time cell activity on the scale of seconds and a longer-term gradually evolving temporal context, and this information then reaches the hippocampus where it is bound to memory (Tsao, A., Sugar, J., Lu, L., Wang, C., Knierim, J.J., Moser, M., and Moser, 2018). Recent work in humans has found evidence suggesting that item and temporal coding exists in LEC (Thavabalasingam et al., 2019). Differences in pre- and post-learning pattern similarity in LEC was found to be correlated with temporal distance

between object pairs in a navigation task (Bellmund, Deuker, & Doeller, 2019). Further work will provide more information of LEC's role in memory.

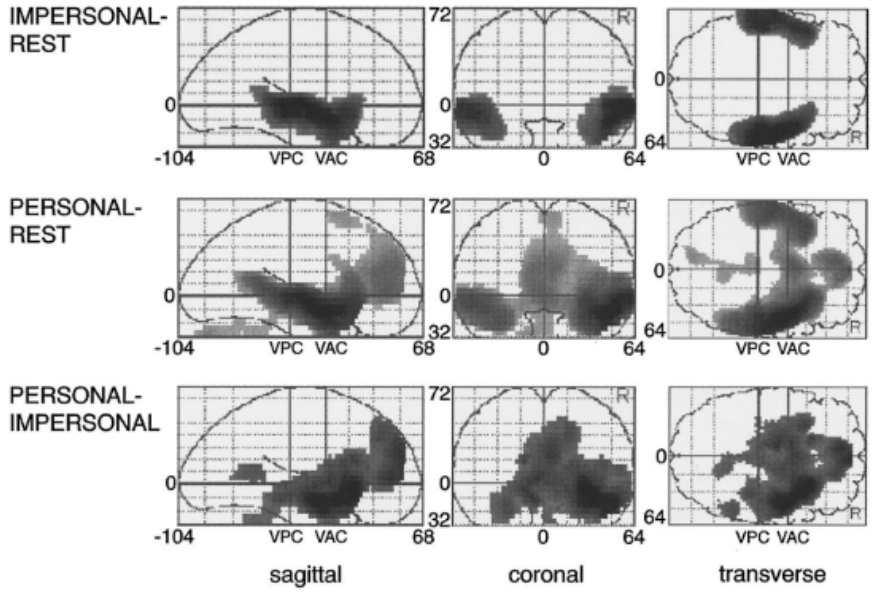


Figure 4: Relative regional cerebral blood flow increases during nonautobiographical (top) and autobioographical (middle) memory retrieval. Bottom row represents autobiographical retrieval minus nonautobiographical retrieval. Adapted from Fink, Markowitsch, & Reinkemeier et al. (1996).

More Naturalistic Experimental Paradigms

Summary of Findings

The ultimate goal of memory research is the understand how the brain allows us to form and retrieve memories from our life experiences. However, when memory tasks in humans typically involve viewing objects on a computer screen, it is unclear how the results apply to memory for vivid everyday, multisensory events. Recently, there have been an increasing amount of studies that use more naturalistic experimental paradigms, from watching videos to having participants wear cameras that take photographs at regular intervals. These experiments provide meaningful information to help the field understand the differences between traditional laboratory and more naturalistic paradigms and how both types of studies can add different pieces to our knowledge.

One study found that the difference in neural activity was mainly in magnitude, with recall of autobiographical memories eliciting greater activity in medial prefrontal cortex, visual and parahippocampal regions, and the hippocampus (Cabeza et al., 2004). However, several studies have found differences in patterns of brain activity between laboratory recognition tests and tests of autobiographical memory (**Figure 4**), suggesting that findings from one may not translate to the other (Fink et al., 1996; Gilboa, 2004; McDermott, Szpunar, & Christ, 2009; Nyberg, Forkstam, Petersson, Cabeza, & Ingvar, 2002). It remains unclear how viewing items on a computer screen differs from viewing videos, in terms of the neurobiological correlates of memory. Until we better understand differences between memory experiments involving items and more naturalistic stimuli, caution should be exerted in overgeneralizing findings from studies using static images or other unisensory stimuli.

Video clips represent an increase in complexity compared to the use of static images. They can be short and have a clearly identifiable theme or action (such as someone putting a loaf of bread into the oven), while still being more multisensory and meaningful than a static image. Recent studies involving videos have yielded important insights into the neurobiological and behavioral correlates of memory. An investigation of temporal order discrimination found that participants took longer to discriminate between events that occurred closer together in time, and vice versa (Kwok & Macaluso, 2015b). The

hippocampus interacts more with default mode network regions when recalling day-old memories of events than when those same events occurred a few minutes earlier (Chen et al., 2016). Researchers were able to decode which video clip participants were recalling, based on BOLD fMRI activity patterns in the hippocampus (Chadwick, Hassabis, Weiskopf, & Maguire, 2010).

Films with certain characteristics show high inter-subject correlation of brain activity (Hasson et al., 2008), which can be leveraged to test hypotheses about memory. A study testing different aspects of memory for video clips found that the precuneus was activated during temporal order retrieval, the superior parietal cortex was activated for spatial judgments, and the medial frontal cortex was activated during scene recognition (Kwok & Macaluso, 2015a).

If the ultimate goal is to understand memory for real-life experiences, researchers should test memory for experiences as close to real-life experiences as possible. Using confederates, or actors, to create memories in participants is the most difficult to control but also the most naturalistic type of memory experiment. In one study, researchers tested memory for a conversation between a confederate and the experimenter in the same room as the participant. Half were told there would be an interruption and to remember, the rest were incidental. They found that young adults made more errors in the incidental condition (West & Stone, 2013).

Another experiment investigated how real-life events are compressed in memory. They had participants wear a camera to give experimenters concrete timing information for events. Interestingly, they found that memory compression was affected by goal processing and perceptual changes (Jeunehomme & D'Argembeau, 2018), two variables that would be almost impossible to test in traditional laboratory experiments. Many of these studies are behavioral, likely due to the difficulty of combining neuroimaging with complex encoding procedures involving confederates.

One study took a slightly different approach and had participants take a museum tour, then were exposed to either exhibits they had seen or lures (reactivation phase) and asked to make ratings on to what extent they were reliving the experience. Finally, their memory was tested inside the MRI scanner. Researchers found that distinct patterns of neural activity at reactivation predicted whether they would show memory distortions at test (St. Jacques, Olm, & Schacter, 2013). This suggests that remembering an experience may set processes in motion that either keep memory veridical or distort it. It is also possible that these neural signatures reflect processes that have already occurred. Regardless, this is an interesting finding that can be more easily generalized to eyewitness testimony than distinguishing static images of one toaster oven from another.

Strengths and Drawbacks

There can be a tradeoff between how real life-like an experience is and how well different aspects of it can be controlled. This is especially challenging if the goal of the experiment is to understand encoding, since it is almost impossible to have a real-life experience inside the MRI scanner, unless approximated by virtual reality. As more research is conducted and the field comes to understand how differences between real-life and virtual reality experiences affect interpretations of results, this will become less of a problem.

It is much more straightforward understand retrieval processes. Researchers can have real life-like encoding sessions and then conduct memory tests in conjunction with their neuroimaging method of choice. For example, one could facilitate a conversation between a confederate and a participant. Then, inside the MRI scanner, one could prompt the participant to indicate whether a series of phrases were said, or if facts from the conversation are true or false. Although it can be challenging to develop, implement, and analyze real life-like experiences for memory research, increasing numbers of recent studies are doing just that. By integrating these findings with traditional laboratory human and animal work, the field will gain a better understanding of how the two compare and can be reconciled to give a more complete picture of how episodic memory works.

Future Directions

The study of memory for real-life events can be viewed as a spectrum, from remembering a list of words or fractals to using actors or confederates to guide participants through rich episodic experiences. Given findings that patterns of neural activity as well as behavioral responses differ based on how real-life like the paradigms are, it seems prudent to move in the "real life-like" direction to the extent this is possible while maintaining control of critical variables and potential confounds. The current study used a more naturalistic stimulus (an episode of a sitcom) in an attempt to better simulate real-life experiences. It combines multi-sensory, dynamic stimuli at encoding with still-frame images at test. This allowed us to approximate complex everyday experiences at encoding while maintaining experimental control at test.

CHAPTER 2: LEC SUPPORTS PRECISE TEMPORAL MEMORIES

N.B. All findings in this study have been published in Montchal, Reagh, and Yassa (2019)

Abstract

There is accumulating evidence that the entorhinal-hippocampal network is important for temporal memory. However, relatively little is known about the precise neurobiological mechanisms underlying memory for time. In particular, whether the lateral entorhinal cortex is involved in temporal processing remains an open question. During high-resolution fMRI scanning, participants watched a ~30-minute episode of a television show. During test, they viewed still-frames and indicated on a continuous

timeline the precise time each still-frame was viewed during study. This procedure allowed us to measure error in seconds for each trial. We analyzed fMRI data from retrieval and found that high temporal precision was associated with increased BOLD fMRI activity in the anterolateral entorhinal (a homologue of the lateral entorhinal cortex in rodents) and perirhinal cortices, but not in the posteromedial entorhinal and parahippocampal cortices. This suggests a novel role for the lateral entorhinal cortex in processing of high-precision minute-scale temporal memories.

Introduction

The association of temporal and spatial contextual information with an experience is a critical component of episodic memory(Ekstrom & Bookheimer, 2007; Ekstrom & Ranganath, 2018.; Kesner & Hunsaker, 2010). A rich literature has examined how spatial properties are encoded by hippocampal-entorhinal circuitry, including spatially selective cells both in the hippocampus (Hartley, Lever, Burgess, & O'Keefe, 2013) as well as the medial entorhinal cortex (MEC) (Hafting, Fyhn, Molden, Moser, & Moser, 2005; McNaughton, Battaglia, Jensen, Moser, & Moser, 2006; Save & Sargolini, 2017). Temporal coding properties in the same network have only been recently examined. The discovery of "time cells" in hippocampal CA1 and MEC (Kraus et al., 2015; MacDonald et al., 2013, 2011; Pastalkova, E., Itskov, V., Amarasingham, A., and Buzsáki, 2008) suggests that the medial temporal lobes (MTL) may employ similar mechanisms and shared circuitry to encode both space and time (Howard Eichenbaum,

2017; Kraus et al., 2015; Salz et al., 2016). In contrast to the MEC, the lateral entorhinal cortex (LEC) appears to code for several elements of the sensory experience (Deshmukh & Knierim, 2011), including item information (Knierim, Neunuebel, Deshmukh and locations of objects in space (Deshmukh & Knierim, 2011). Human fMRI studies have similarly shown that the LEC is preferentially selective for object identity information (i.e. “what”), whereas the MEC is preferentially selective for spatial locations (i.e. “where”) (Murray & Yassa, 2017; Reagh & Yassa, 2014). Whether the LEC provides temporal information to or receives information from the hippocampus to become integrated in episodic representations remains an open question. While the temporal coding properties of “time cells” offer a suitable mechanism by which short timescales (milliseconds to seconds) may be encoded, it is not clear how the longer timescale of episodes (minutes) are encoded by these mechanisms. Additionally, episodic memory involves unique “one-shot” encoding that is incidental in nature, while most studies assessing temporal coding properties involve explicit tasks and/or extensive training (e.g. sequence learning). We address both of these challenges by using a 30-minute incidental viewing paradigm of a complex naturalistic stimulus (an episode of a television sitcom) and a continuous evaluation of the precision of subsequent temporal memory judgments (on the order of seconds to minutes). Here, we demonstrate that the LEC plays a prominent role in temporal processing in a task involving a timescale of minutes. These results suggest that there may be multiple

distinct mechanisms supporting temporal memory in the MTL and that timescale may be a critical variable that should be considered in future work.

Materials and Methods

Participants

Twenty-six healthy adult volunteers were recruited from the University of California, Irvine and the surrounding community. They gave informed consent in accordance with the Institutional Review Board at the University of California, Irvine and received monetary compensation. All participants were right handed and were screened for psychiatric disorders. Six were excluded due to excessive motion (>20% of TRs excluded due to the Euclidian Norm of the motion derivative exceeding 0.3mm), and one requested to stop the study after the first functional scan. Data from the remaining 19 participants (10 female, ages 18-29 [mean 21.42, SD = 2.85]) was analyzed. Sample size was calculated a priori based on power analyses which demonstrate that for high resolution functional MRI studies, a minimum of 16 subjects is required to achieve 80% power at an alpha of .05.

Functional MRI task

Encoding: Participants viewed an episode of Curb Your Enthusiasm (Season 2 Episode 9 “The Baptism”) while in the MRI scanner. This was presented using PsychoPy (Pierce et al., 2019) version1.82.01. The episode was split into three equal parts, each 9

minutes and 26 seconds long (**Figure 5**). Participants were instructed to pay attention to the videos and that they would be asked questions about them later. After each video segment, we collected a 5-minute resting state scan in which participants were instructed to look at a fixation cross in the middle of the screen.

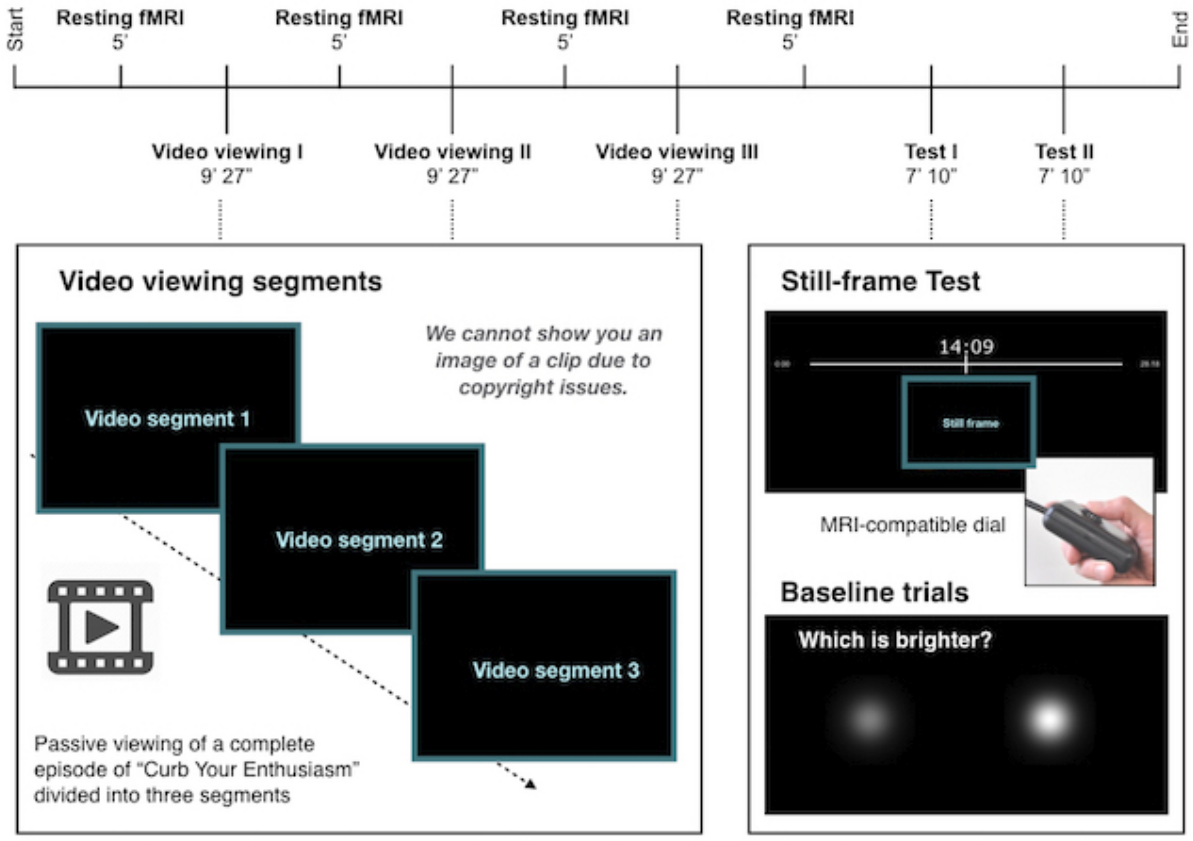


Figure 5: Schematic of the experimental design. Participants watched an episode of Curb Your Enthusiasm, then were asked to place still frames from the episode on a timeline while inside the MRI scanner.

Retrieval: Retrieval took place approximately 5 minutes after the last resting state scan at encoding. During each of 2 runs, participants were presented with 72 still frames from

the video segments and were asked to indicate when during the episode they thought each still frame occurred. Above each still frame, a timeline appeared that ranged from 0 seconds (beginning of the episode) to 28:18 seconds (the end of the episode). No still frames from the first or last minute of the episode were used to avoid primacy/recency effects. A cursor was visible and moved in sync with an MR-compatible scroll click device that is similar to the scroll wheel on a mouse (Current Designs). On perceptual baseline trials, two gray circles appeared on the screen and participants were instructed to indicate which circle was brighter. Each of these trials were 9 seconds long, and they comprised 25% of total retrieval trials. Outside of the scanner, participants took a test about events that occurred during the episode. All reported analyses were performed on retrieval data only.

Behavioral Control Experiment

In order to ensure that participants were performing adequately on the task, we conducted a behavioral experiment on a separate group of participants. These participants did not watch the episode of Curb Your Enthusiasm. They were asked to place the still frames from the episode on a timeline without ever having watched the episode. Because they were not able to use memory to guide their responses, their performance is considered to be at chance. We then performed a Kolmogorov–Smirnov test using GraphPad Prism (Graphpad Software, La Jolla CA USA, www.graphpad.com)

to determine whether performance from this experiment was significantly different than that of the actual fMRI participants (**Figure 6**).

MRI acquisition

Neuroimaging data were acquired on a 3.0 Tesla Philips Achieva scanner, using a 32-channel sensitivity encoding (SENSE) coil at the Neuroscience Imaging Center at the University of California, Irvine. A high-resolution 3D magnetization-prepared rapid gradient echo (MP-RAGE) structural scan (0.65 x 0.65 x 0.65mm) was acquired at the beginning of each session and used for co-registration. Each of two functional MRI scans consisted of a T2*-weighted echo planar imaging (EPI) sequence using blood-oxygenation-level-dependent (BOLD) contrast: repetition time (TR)=2500 ms, echo time (TE)=26 ms, flip angle = 70 degrees, 33 slices, 172 dynamics per run, 1.8 × 1.8 mm in plane resolution, 1.8 mm slice thickness, field of view (FOV) =180 x 65.8 x 180. Slices were acquired as a partial axial volume and without offset or angulation. Four initial "dummy scans" were acquired to ensure T1 signal stabilization.

Functional MRI Analysis

Preprocessing: Preprocessing and general linear model analysis was conducted using AFNI (Analysis of Functional NeuroImages) software (Cox, 1996). First, data were brain extracted (3dSkullStrip). Then, using afni_proc.py, TRs pairs where the Euclidian Norm of the motion derivative exceeded 0.3mm were excluded from the analysis. Functional

data were slice timing corrected (3dTshift), motion corrected (3dvolreg), and blurred to 2mm (3dmerge). Each subject's functional data was aligned to their anatomical scan (3dallineate). Then, we used ANTs (Advanced Normalization Techniques) software (Avants, Tustison, & Song, 2009) to align each subject's data to a common template (0.65mm isotropic).

General Linear Model: For each subject, retrieval trials were ordered by the amount of error in seconds (distance between the subject's response and the correct answer). The ordered trials were then split into three conditions: high precision, medium precision, and low precision trials. These three conditions were entered into the general linear model using 3D deconvolution in AFNI (3dDeconvolve), in addition to 6-dimensional motion regressors generated during motion correction. We restricted our analysis to task-activated voxels which we obtained by thresholding the full F-statistic containing all experimental conditions (thresholded at $p = 0.35$, cluster extent threshold = 20), which thus does not bias voxel selection towards any particular condition of interest. Subsequent analyses compared parameter estimates (beta coefficients) from the most and least precise trials, compared to perceptual baseline trials. This was done using the AFNI *3dmaskave* function to extract average beta coefficients across the left and right components of each region.

Regions of interest (ROIs) were traced on the common template (0.65 mm isotropic) to which each subject's data was aligned. Beta coefficients were averaged across all voxels in each ROI (3dmaskave). For each ROI, paired t-tests were conducted on parameter estimates from the most precise and least precise trials. Bonferroni-Holm correction for multiple comparisons was used for clusters of a priori ROIs (hippocampal and medial temporal lobe cortex [CA1, DGCA3, subiculum, alEC, pmEC, PRC, and PHC] and other cortical regions (RSC, medial prefrontal cortex, angular gyrus, PCC, and PreC]). Cohen's d was calculated for significant effects using the formula (Mean1-Mean2)/pooled standard deviation.

Still frame presentation was pseudo-randomized for each participant, using PsychoPy (Pierce et al., 2019). Otherwise, "high", "medium" and "low" precision conditions were based on participant performance and therefore could not be randomized. Data collection and analysis were not performed blind to the conditions of the experiments.

Statistics

We conducted the Kolmogorov-Smirnov test using GraphPad Prism (GraphPad Software, La Jolla, CA USA, www.graphpad.com). This software was also used for the following analyses: 1) to compare BOLD fMRI activity for high and low precision trials using two-tailed paired-samples t-tests, 2) to conduct a one-way repeated measures ANOVA comparing trials with short, medium, and long distances from video boundaries,

and 3) to compare BOLD fMRI activity for high and low vividness trials using two-tailed paired-samples t-tests. To assess whether modulation scores (high-low precision beta coefficients) were significantly different from 0, we used Rstudio (2015) to conduct one-sample t-tests. Data distribution was assumed to be normal but this was not formally tested. Individual data points are shown for every analysis. Sample size was calculated a priori based on power analyses which demonstrate that for high resolution functional MRI studies, a minimum of 16 subjects is required to achieve 80% power at an alpha of .05.

Results

Temporal judgments generate a range of accuracies between 1-3 minutes

During fMRI scanning, subjects watched a ~30-minute television episode of a sitcom (Curb Your Enthusiasm, HBO), and were asked during a later test to determine, on a continuous timeline, *when* still-frames extracted from the episode appeared during incidental viewing (**Figure 5**). All analyses discussed were performed on data at retrieval. To ensure that subjects are able to accomplish the task and that behavioral performance reflects a range of different accuracies we quantified error in seconds on each trial. Average error was 155.54 seconds (2.6 minutes), with a standard deviation of 163.58 seconds (**Figure 6**). In each subject, we divided retrieval trials into thirds: “high precision”, “medium precision” and “low precision” trials. Across subjects, “high precision” trials were associated with error < 74 seconds and “low precision” trials were

associated with error > 170 seconds, suggesting that the differences in terms of time were not drastic. In other words, the comparison is akin to examining differences in being accurate within a minute vs. three minutes. Trials with error exceeding five minutes were rare across all subjects and did not contribute significantly. Additionally, we ascertained that all participants were attentive to the episode and evaluated their semantic knowledge of the episode using a post-scan true-false test. Average accuracy was 96%. To further determine whether similar accuracy could be driven by response biases (preference for specific portions of the timeline) or other factors not associated with temporal memory, we conducted a separate control experiment in an independent sample. Subjects in this experiment did not watch the episode but were still asked to place the still-frames on the timeline.

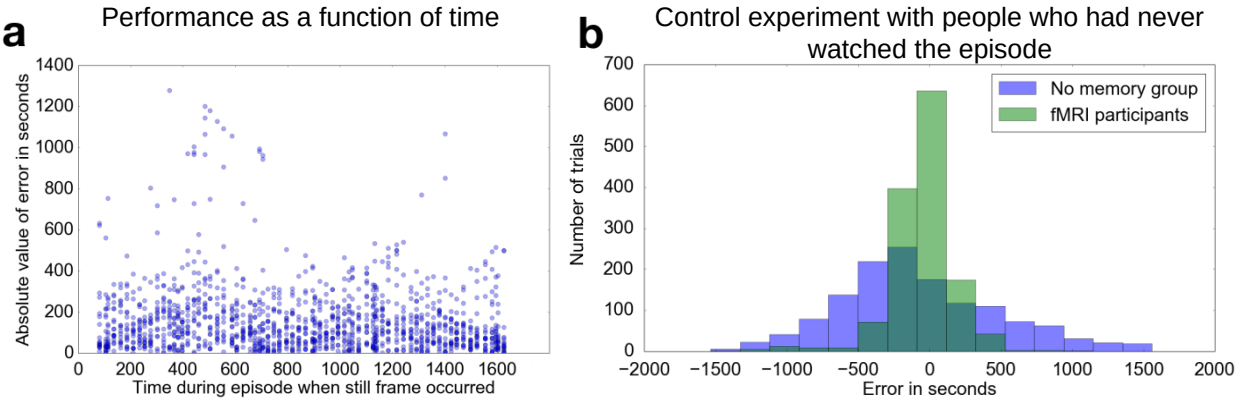


Figure 6: Behavioral performance on the task. a) Error as a function of the time at which each still frame was viewed during the episode. b) Data from the behavioral control experiment, with the no-memory gorup in purple and fMRI participants in green.

Because they had no memory for the episode, their performance provided a measure of the random distribution. We compared the distribution of accuracy (absolute value of the trial-by-trial error in seconds) in the experimental fMRI sample and the control sample that did not view the episode using a nonparametric two-tailed Kolmogorov-Smirnov test. The difference across the two distributions was significant (K-S D=0.4991, p<0.0001), **Figure 6**), confirming that performance in the fMRI participants was not merely reflecting behavioral biases related to assessment via the continuous timeline. We conducted a one-way repeated measures ANOVA comparing trials that were of short (2-107 seconds), medium (108-186 seconds) and long (200-277 seconds) distances from a boundary, which was not statistically significant [F(2,18)= 3.29 , p>0.05], indicating that error does not differ significantly based on a trial's distance from a segment boundary (**Figure 7**).

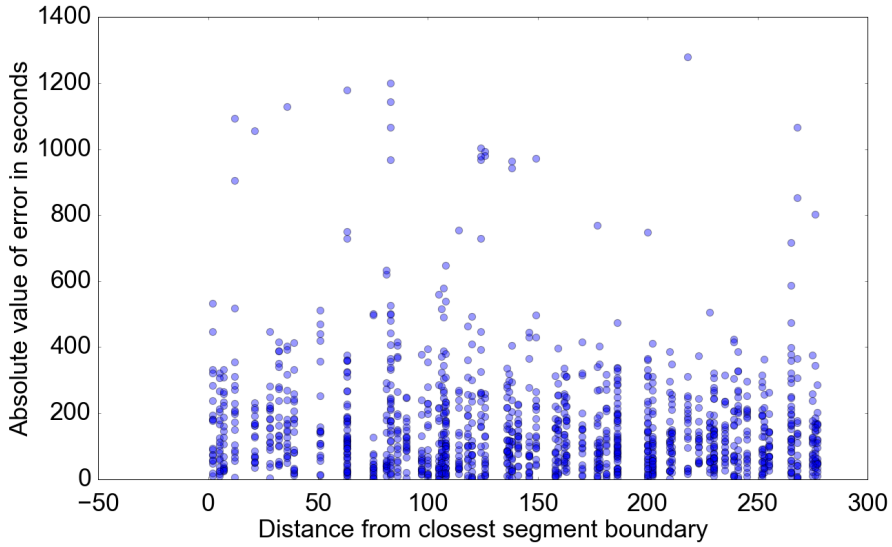


Figure 7: Effect of distance from boundary on memory performance. A one-way repeated-measures ANOVA was conducted to determine whether performance differed as a function of each trial's distance from a segment boundary at encoding (n=19 participants). A segment boundary is defined as the beginning or end of a video segment at encoding (the episode was split into three segments). We conducted a one-way repeated measures ANOVA comparing trials that were of short (2-107 seconds), medium (108-186 seconds) and long (200-277 seconds) distances from a segment boundary, which was not statistically significant [F(2,18)= 3.29 , p=0.0506], indicating that error does not differ significantly based on a trial's distance from a segment boundary.

Additionally, we found no evidence for regional modulations by vividness of the recall. We asked twelve participants to provide vividness ratings after the scanner-based

recall and compared high vs. low vividness trials. We found no significant differences that surpassed our cluster-based threshold of $p < 0.05$ (**Figure 8**).

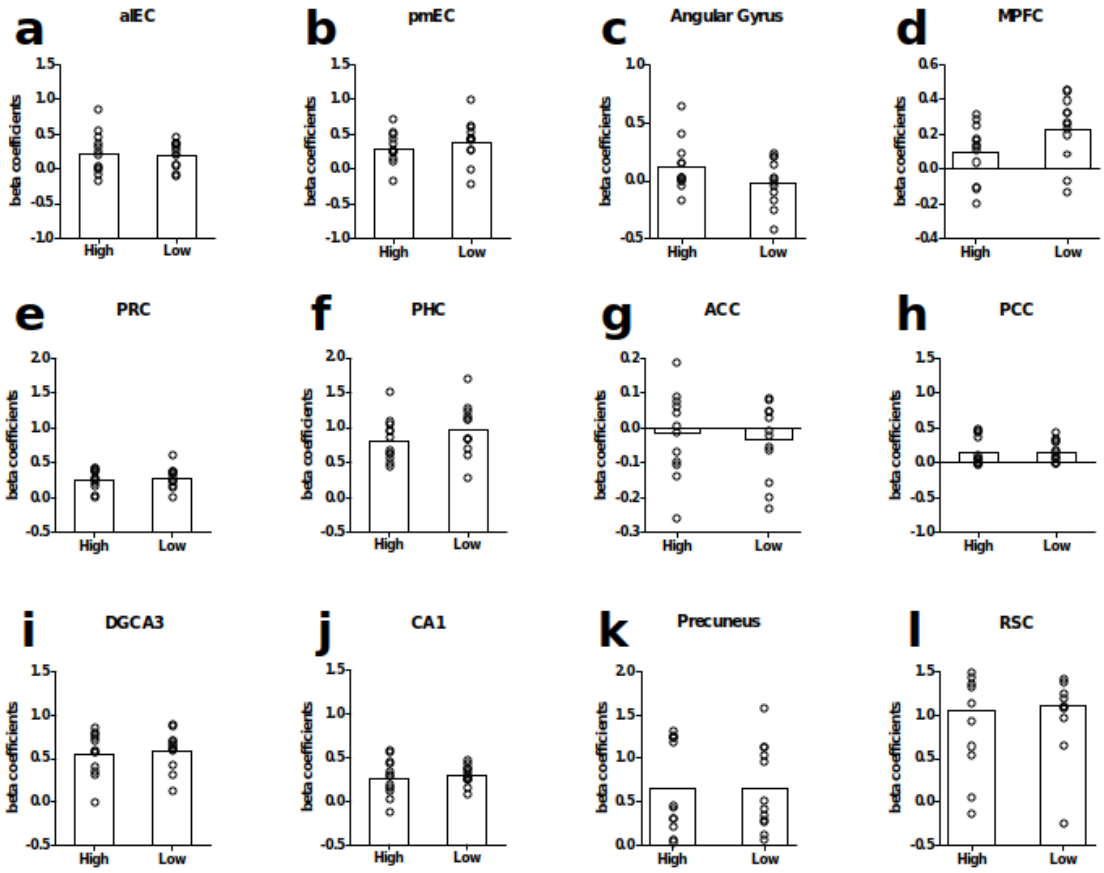


Figure 8: Effect of vividness on MTL and cortical regions. After scanning, participants viewed the still frames one more time and were asked to indicate how vividly they could recall the scene associated with each one on a 5 point scale (n=12 participants). High, medium, and low vividness trials were entered into a GLM. Paired t-tests were conducted on high and low vividness beta coefficients, and no significant results were found after correcting for multiple comparisons using the Bonferroni-Holm method in the aIEC [t=0.4983, df=11, two-tailed p=0.6281], pmEC [t=1.947, df=11, p=0.0774], angular gyrus [t=3.06, df=11, p=0.0109], MPFC [t=2.956, df=11, two-tailed p=0.0131; critical p is 0.0083], PRC [t=0.4744, df=11, two-tailed =0.6445], PHC [t=1.976, df=11, two-tailed p=0.0738; critical p is 0.01], ACC [t=0.5422, df=11, two-tailed p=0.5985], PCC [t=0.1654, df=11, two-tailed p=0.8716], DGCA3 [t=0.7672, df=11, two-tailed p=0.4591], CA1 [t=0.6167, df=11, two-tailed p=0.549], precuneus [t=0.3441, df=11, two-tailed p=0.7373], RSC [t=0.703, df=11, two-tailed p=0.4967]).

Anterolateral but not posteromedial EC is selectively engaged for precise temporal memory

Recent work using fMRI functional connectivity has clarified the boundaries of the LEC and MEC regions in the human brain and demonstrated that, consistent with nonhuman primate anatomical studies (Suzuki & Amaral, 1994), the human analog of rodent LEC is anterolateral (alEC), whereas the human analog of rodent MEC is posteromedial (pmEC (Maass, Berron, Libby, Ranganath, & Düzel, 2015; Schröder, Haak, Jimenez, Beckmann, & Doeller, 2015). We used anatomical masks for alEC and pmEC to contrast the level of engagement as a function of temporal precision in these two particular regions. Contrasting high vs. low precision trials allowed us to examine sensitivity of MTL regions to the temporal accuracy of recall. Voxel beta coefficients were averaged within the regions of interest as an overall indicator of the degree of model fit with the underlying hemodynamic signal. We found significant temporal precision-related modulation in the alEC ($t=4.537$, $df=18$, two-tailed $p=0.0003$, Cohen's $d=0.8808$, **Figure 9a**) but not in the pmEC ($t=0.3504$, $df=18$, two-tailed $p=0.7301$, **Figure 9b**). To determine if this difference across subregions of the EC was significant, we calculated the difference in beta coefficients between high and low precision conditions and contrasted the alEC and pmEC on this difference measure (i.e. modulation score). We found that the difference in modulation score was also significant ($t=4.794$, $df=18$, two-tailed $p=0.0001$, Cohen's $d=1.0886$, **Figure 9c**), suggesting that high precision trials preferentially engaged the alEC but not pMEC. To determine if this

selective engagement may extend upstream of the entorhinal cortex, we additionally averaged voxel activity in the perirhinal (PRC) and parahippocampal (PHC) cortices. As expected from the EC results, upstream cortices reflected a similar effect. We found a significant difference between high and low precision trials in the PRC (t=4.331, df=18, two-tailed p=.0004, Cohen's d=0.8936, **Figure 9d**) but not in the PHC (t=0.1464, df=18, two-tailed p=0.8852, **Figure 9e**). Modulation scores across the two regions were also significantly different (t=3.193, df=18, p=.0005, Cohen's d=0.7213, **Figure 9f**). Together, these results suggest that the extension of the ventral visual stream (PRC and alEC) is engaged in temporal processing on the scale of minutes, whereas the extension of the dorsal visual stream (PHC and pmEC) does not appear to show temporal precision-selective signals on the same scale.

Hippocampal DG/CA3 is more engaged than CA1 for precise temporal memory

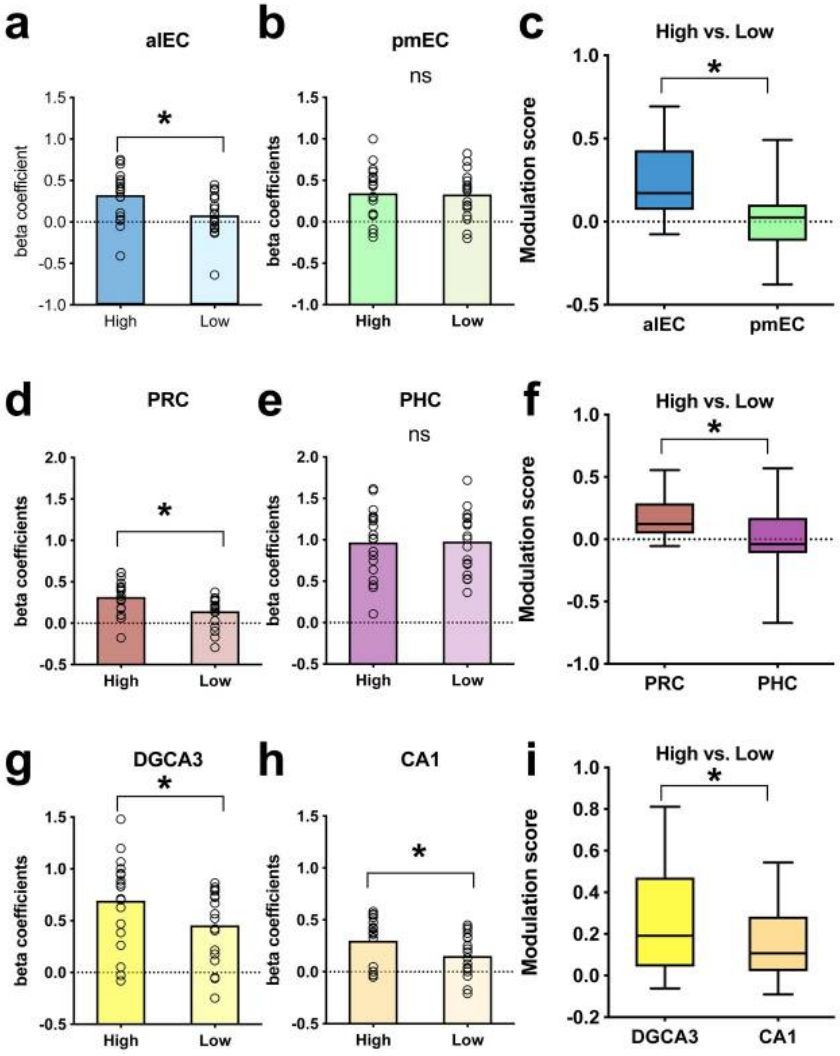


Figure 9: Effects of precision on MTL regions. (a,b,d,e,g,h) Comparing most precise [within 1 min] > least precise [over 3 min] across hippocampal subfields and MTL cortical regions; Using two-tailed paired t-tests, we found significantly higher BOLD fMRI activity for high vs. low precision trials in alEC (t=4.537, df=18, two-tailed p=0.0003), PRC (t=4.331, df=18, p=0.0004), DGCA3 (t=4.113, df=18, p=0.0007), and CA1 (t=3.691, df=18, two-tailed p=0.0017). No significant differences were found in pmEC (t=0.3504, df=18, p=0.7301) and PHC (t=0.1464, df=18, p=0.8852). n=19 for all comparisons. (c,f,i) Magnitude of modulation by precision. Difference metrics were calculated by subtracting beta coefficients from the 'least precise' condition from those of the 'most precise' condition. Modulations were significantly higher in the alEC (t=4.794, df=18, two-tailed p=0.0001), PRC (t=3.193, df=18, p=0.0005) and in hippocampal subfields (with a stronger effect in DG/CA3; t=3.091, df=18, p=0.0063) compared to the pmEC, PHC, and CA1.

Next, we sought to examine whether hippocampal subfields show BOLD fMRI signals modulated by the precision of temporal judgments. We used anatomical segmentations of hippocampal dentate and CA3 (combined for a joint DG/CA3 label as in past fMRI studies), and CA1 to get regional averages of voxel-level activation during temporal memory judgments. We found precision-related modulations (high vs. low) in both hippocampal subregions, with stronger effects in DG/CA3 (t=4.113,

df = 18, two-tailed p=0.0007, Cohen's d=0.622, **Figure 9g**) compared to CA1 (t=3.691, df=18, two-tailed p=.0017, Cohen's d=0.6871, **Figure 9h**). Again, we calculated average modulation scores across the two subregions across all participants and found a significant difference across subfields (t=3.091, df=18, two-tailed p=0.0063, Cohen's d=0.4216, **Figure 9i**), suggesting that the modulation by temporal precision in DG/CA3 was stronger than in CA1.

Cortical regions preferentially engaged during precise temporal memory judgments

Since correct temporal memory judgments would be expected to engage circuitry involved in the experience of recollection and memory for rich contextual details, we examined how cortical regions outside of the MTL are modulated by temporal memory precision, focusing on regions previously implicated in recollection and detail memory (Ranganath & Ritchey, 2012), including the angular gyrus (AG), retrosplenial cortex (RSC), precuneus (PreC), posterior cingulate cortex (PCC), and medial prefrontal cortex (mPFC). Using anatomical masks for these regions to average voxel-level activity during high and low precision, we found significant high vs. low differences bilaterally in the mPFC (t=3.851, df=18, p=0.0017, Cohen's d=0.6469), the AG (t = 3.41, df = 18, p = 0.0031, Cohen's d=0.6471), and the PCC (t=2.75, df=18, p=0.0132, Cohen's d=0.4547). We observed no significant modulation in the precuneus (t=1.937, df=18, p=0.068) and retrosplenial cortex (t=0.137, df=18, p=0.8925). These results are summarized using modulation scores across cortical regions (**Figure 10**). Collectively, analyses of cortical

regions suggest that memories recollected with higher temporal precision engage some of the same cortical circuits and regions known to play a role in the representation of detail memory.

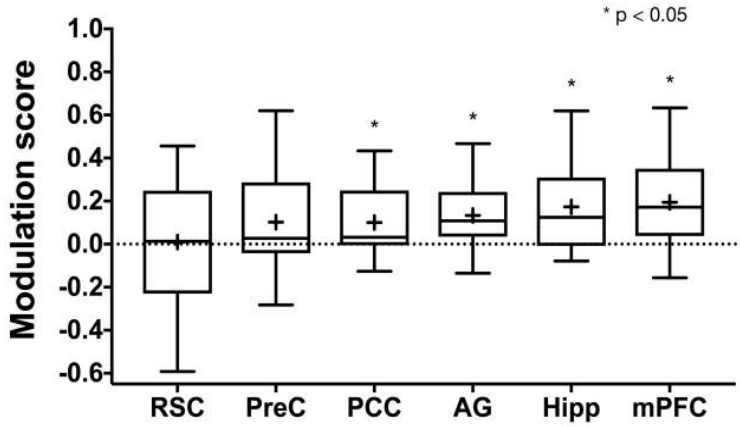


Figure 10: Cortical reinstatement effects.(a) Cortical temporal modulation scores across regions previously implicated in recollection and recall of contextual or detail memory including the retrosplenial cortex (RSC, t=−0.0027, df=18, p=0.9979), precuneus (PreC, t=1.685, df=18, p=0.1093), posterior cingulate cortex (PCC, t=2.7984 df=18, p=0.0119), angular gyrus (AG, t=3.3742, df=18, p=0.0034), medial prefrontal cortex (mPFC, t=2.899, df=18, p=0.0096), and the whole hippocampus (Hipp, t=3.9518, df=18, p=0.0021) for reference.

Discussion

Results from this study suggest that temporal precision judgments on the order of minutes are associated with increased BOLD fMRI activity in the alEC and PRC, which is consistent with a broad role for these regions in the processing of external input including information about temporal context. The observation that alEC-PRC network but not the pmEC-PHC network was significantly more engaged for trials with high temporal precision suggests that distinct mechanisms may be used to process and store spatial and longer-timescale temporal information. Past studies in rodents have demonstrated little spatial selectivity in LEC but strong coding for object properties (Deshmukh & Knierim, 2011; Knierim et al., 2014). One study which used a similar timeline asked participants to make retrospective estimates of the duration of time between audio clips from a radio story. They found that these

duration estimates correlated with BOLD fMRI pattern similarity in the right entorhinal cortex, though the authors did not segment aLEC and pMEC (Lositsky, Chen, Toker, Honey, Shvartsman, et al., 2016). More recently, an examination of LEC firing properties during open exploration has demonstrated strong temporal coding on the order of minutes, consistent with our results (Tsao et al., 2018).

The observation that PRC was significantly more engaged for the most temporally precise trials was only partially consistent with prior studies. Inactivation of the PRC in rats has been associated with impaired temporal order memory for objects (Hannesson, 2004) and a subset of neurons in the PRC alter their firing based on how recently an object was viewed (Hannesson, 2004). In contrast, a number of studies have demonstrated a role for the PRC in object recognition and not the recall of contextual details *per se* (Eichenbaum, Yonelinas, & Ranganath, 2007). Studies in humans using fMRI have reported signals linked to temporal context, operationalized in terms of items' ordinal positions in a sequence, in the PHC and not the PRC (Hsieh et al., 2014; Jenkins & Ranganath, 2010; Tubridy & Davachi, 2011b). It is worth noting that these prior studies used a short timescale of event proximity (seconds, not minutes), whereas the current study used a much longer timescale (minutes to tens of minutes). It is possible that coding for temporal relations on this longer timescale may involve distinct mechanisms that are more in-line with the hypothesized functions for the alEC and PRC regions in semantic recall.

Consistent with the possibility that distinct neural mechanisms support short and long timescale temporal coding, we also found no temporally-modulated signals in the PHC, a region that has been associated with fine temporal memory judgments (Tubridy & Davachi, 2011b) on a short timescale. A previous study (Lehn et al., 2009) reported PHC engagement during retrieval of temporal order for events in a television show, but that this activity was not associated with precision, thus it is difficult to draw conclusions about whether the activity supported performance.

Another aspect of this work that differs significantly from extant literature is that all fMRI data discussed are from retrieval, not encoding. Previous research investigating temporal memory and using a timeline (Jenkins & Ranganath, 2010; Lositsky, Chen, Toker, Honey, Shvartsman, et al., 2016) found that fMRI activity at encoding predicted aspects of subsequent temporal memory. In contrast, our work sought to investigate networks that support retrieval of experiences in order to make temporal memory judgments. This difference in experimental design fills a gap in the literature and may partially explain the divergence between the reported results and those of previous studies.

One potential limitation is that the current study and other tasks using naturalistic stimuli are less able to control every aspect of encoding and retrieval. We tried to control for

alternative explanations to the extent that it was possible. One is that our results could have been driven by attention at encoding, with participants preferentially attending to objects in scenes for which they later had greater temporal precision. After they completed the study, we asked twelve of our fMRI participants to rate how vividly they could recall the scene associated with each still-frame image from the experiment (**Figure 9**). We then used those ratings to perform a univariate analysis to test whether there was significantly higher BOLD fMRI activity for high vs. low vividness trials in our ROIs. We found no significant differences, indicating that the most vividly recalled scenes were not associated with higher alEC activity. It is possible that participants' self-reports of vividness were imperfect or that during encoding, participants preferentially attended to certain parts of the video that were later recalled more precisely.

Another potential issue could be that the task primarily taxed memory for details (as opposed to memory for timing information). If this were the case, we would expect high-precision trials to also be recalled more vividly. However this was not the case, as explained above. Additionally, some of the brain regions active preferentially for the highest temporal precision trials have previously been found to be selectively involved in temporal memory. One study showed that the angular gyrus was activated more for a temporal task compared to spatial or object tasks (Kwok & Macaluso, 2015a). Future

studies could explicitly test memory for details in addition to temporal memory, to explore potential differences or overlap between these two mnemonic functions.

The reader may wonder why high precision trials were associated with increased BOLD fMRI activity in certain areas and what that can be interpreted to mean. When brain regions are activated, this is associated with increased blood flow which can be detected through fMRI. The increased activation observed in alEC, PRC, the hippocampus, and cortical regions may be the result of more reactivation for those trials. In other words, at high temporal precision trials, these regions are likely working together to reactivate many of the same neurons that were active when participants were viewing the episode, allowing them to recall when the still frame happened. A complicating factor is that there is evidence that the hippocampus is also involved in mental imagery and imagination (Maguire & Hassabis, 2011). However, there is also evidence that the medial temporal lobe is more activated for true than false memory (Kim & Cabeza, 2007), although activation should not be used as a metric to determine veracity of information being recalled. Since these regions showed greater activity for high temporal precision trials, we hypothesize that this increased activity correlates to recalling the scene and reinstating the temporal context.

Overall, naturalistic tasks and tightly controlled laboratory tasks each have different strengths and weaknesses. Tightly controlled laboratory experiments are less

generalizable to real-life situations. We controlled for potential confounds as much as possible, by choosing an episode from a television show that uses situational humor that requires an understanding of the characters and the narrative, has been used in the past by other investigators (Furman, Dorfman, Hasson, Davachi, & Dudai, 2007), takes place in a relatively small number of physical locations, and does not include a laugh track. Integrating evidence from both naturalistic and laboratory studies will advance understanding of memory systems.

It is important to consider the relative contributions of pure timing information vs. sequence/event information in determining when events occurred. This is especially true for more naturalistic paradigms involving multisensory information, since events can be salient and have meaning. It is likely that both types of information are important for making temporal judgments. It would be useful for future studies to compare memory for events that occur in a meaningful order with events that have less of a sequential structure.

Our results demonstrate a prominent role for the alEC and PRC in temporal memory on the scale of minutes. This demonstration also brings timescale into consideration as a potential critical variable in studying temporal memory that may affect which brain networks are recruited to support encoding and retrieval. Single MTL neurons fire at a preferred time during trials lasting a few seconds (MacDonald et al., 2011). However, it

is likely that a gradually changing pattern from many MTL neurons would be necessary to encode longer time periods (minutes to days). Experiences that span minutes to hours are likely associated with evolving internal states (wake/sleep cycles, hunger, etc.) that may help in distinguishing them from similar experiences that occurred at different times. Further work will be necessary to elucidate the specific molecular and synaptic mechanisms that underlie temporal storage and retrieval at these different timescales.

In order to confirm the role of these regions in memory for time, future work should directly contrast brain activity associated with high precision memory for time with other types of memory (such as spatial or detail memory). Data showing greater alEC activation for correct temporal vs. correct spatial or object memory would be compelling evidence that this region serves a specific function in memory for time.

Overall, these results should be interpreted in light of the specific experimental parameters of the paradigm. This work differs from the majority of published studies on memory for time in humans, since it tests absolute memory for when events occurred instead of showing two images and asking which was shown first. Another potentially important difference is that this study involves one-shot learning, whereas most studies of temporal memory involve learned sequences. These factors could contribute to the

somewhat surprising results, and further work will elucidate neural correlates of memory for absolute time vs. order and one-shot learning vs. repeatedly viewed stimuli.

CHAPTER 3: EVENT BOUNDARIES AND MEMORY PRECISION

Abstract

To better understand our lives, several theories posit that we separate the continuous stream of our lives into manageable chunks, through a process called event segmentation. Prior work has shown that this process affects memory performance and that people reliably segment events at similar timepoints (Gold, Zacks, & Flores, 2017; Jeunehomme & D'Argembeau, 2018; Magliano & Zacks, 2011; Swallow, Zacks, & Abrams, 2009). Different brain regions also seem to participate in this process passively, by changing their patterns of activity at common event boundaries (Baldassano, Chen, Zadbood, Pillow, & Norman, 2018). The current study tested whether event boundaries affected the precision of memory for when events occurred during a ~30 minute video. We found no differences. We also identified a cluster in the superior temporal gyrus that was preferentially activated at event boundaries.

Introduction

The world around us is constantly changing. Memory is organized in time, but humans can't remember every detail in this continuous stream. In the Zacks et al. (2007) theory of event segmentation, event is defined as "a segment of time at a given location that is conceived by an observer to have a beginning and an end" and can last in the range of

seconds to hours. People make predictions guided by perception, and also using previous knowledge and experiences. When a something unexpected happens, a prediction error occurs and an event boundary is perceived (**Figure 8**).

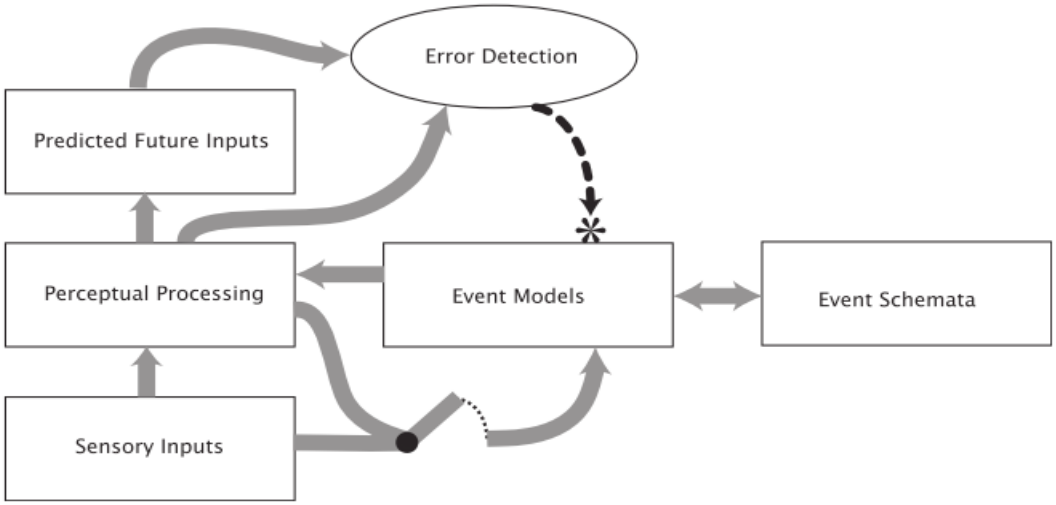


Figure 11: A schematic of event segmentation theory. Thin gray arrows show the flow of information. Dashed lines indicate projections that lead to the resetting of event models. Adapted from Zacks (2007).

Other theories have been proposed to explain how events are processed in the brain. Work from Schapiro et al. (2013) call into question whether error detection is necessary to organize events into meaningful units. They found that participants were able to identify event boundaries in the absence of error detection signals (transition probabilities were uniform).

Another critical feature of organizing events in memory may be changes in contextual stability (Clewett & Davachi, 2017). This is supported by the fact that participants did not

detect when events were presented out of order, suggesting that predictions are not always made and therefore prediction error is not critical to event segmentation or understanding event sequences (Hymel, Levin, & Baker, 2016). Many questions remain regarding what contributes to event boundary decisions and the significance of these boundaries in memory retrieval and behavior.

What does the brain do with a continuous stream of information in the absence of a formal task? One study found that when participants read a story, several regions, such as the posterior cingulate, precuneus, and right posterior superior temporal gyrus showed increased activation at event boundaries (Speer et al., 2007). Ben-Yakov and Henson (2018) investigated patterns of brain activity associated with event boundaries when participants passively viewed a video. They found increased hippocampal activation at event boundaries. Here, event boundaries are defined as meaningful units of activity during the video.

Baldassano et al. (2017) provided further information on neurobiological responses to event boundaries. They found that brain regions (such as the angular gyrus) shift their patterns of activity at event boundaries. Lower-order sensory regions do this for shorter, simpler events, while higher-order brain regions can track more complex and abstract boundaries.

A picture is starting to emerge of how high-order brain regions use event boundaries to segment and learn from our experiences. Combining analysis of neuroimaging data with behavioral measures, such as memory performance, the relationship between event boundaries and memory precision will be better understood. This is the goal of the present study. In this work, event boundaries are defined as scene changes, or times when the characters are moved one location to another. This allows us to investigate how changes in spatial location may affect memory performance for timing information. Behaviorally, we test whether distance from event boundaries affects memory performance. We also identify brain regions sensitive to event boundaries during passive viewing of a video.

Methods and Results

Nineteen participants watched an episode of Curb Your Enthusiasm and answered questions about when events in it occurred, as described in Chapter 2.

Event boundaries

Event boundaries were defined as scene changes, or moments where characters are in a new location and/or time is presumed to have passed. Boundaries were created through combined analysis of participant data and experimenter-identified scene changes. A separate cohort of 33 participants watched the same episode and indicated when they thought a scene change had occurred, by pressing the space bar. These

responses were aggregated and k-means clustering was used to identify common boundary locations. This resulted in 50 total boundaries (see **Figure 12**). One difficulty with event boundaries is that they are most apparent to the observer after the boundary has occurred. Consequently, the experimenter went through the episode to identify boundaries, with the ability to validate boundaries by pausing the video and going forward or backwards in time. Using this technique, we identified 15 boundaries, 93% of which had a participant-identified boundary within 15 seconds of it.

Behavioral analysis: Do scene changes affect temporal memory performance?

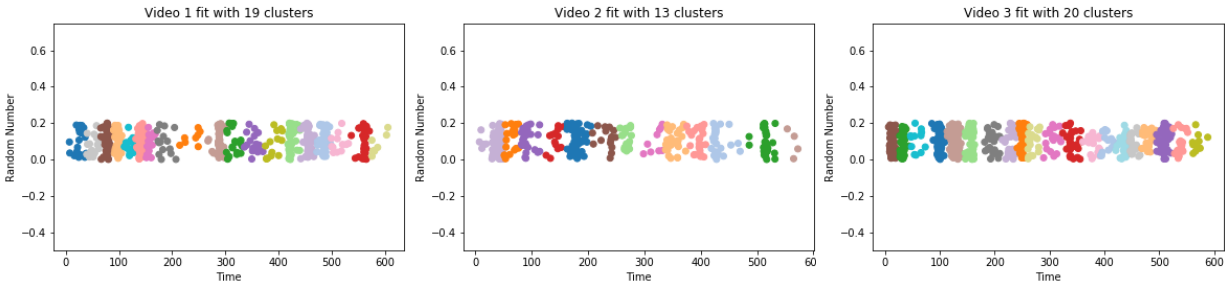


Figure 12: A separate group of participants was asked to identify each scene change during the episode by pressing the space bar. Then, we ran k-means clustering on participant data, resulting in these color-coded groups.

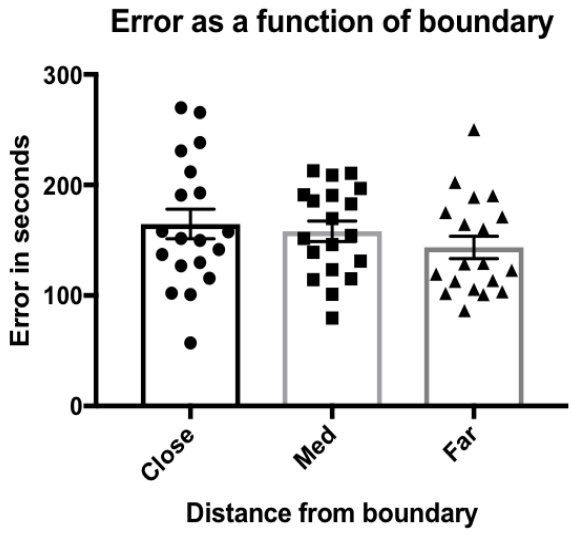


Figure 13: Trials with different distances from an event boundary were not found associated with statistically signficantly different temporal memory performance.

Using the boundaries generated as described above, we calculated the distance of each trial to its closest event boundary. Then, for each participant, trials were split into close (average 9.27 seconds), intermediate (average 39.23 seconds), and far (average

100.56 seconds) distance from a boundary. Graphpad Prism 7 (Graphpad Software, San Diego, CA USA, www.graphpad.com) was used to conduct a repeated-measures ANOVA with a Greenhouse-Geisser correction for sphericity (**Figure 13**). Distance from event boundary was not found to have a statistically significant effect on memory performance ($F(1.78, 32.04) = 2.193$, $p = 0.1329$).

FMRI preprocessing

Data was preprocessed as described in Montchal, Reagh, & Yassa, 2019: Preprocessing and general linear model analysis was conducted using AFNI (Analysis of Functional NeuroImages) software (Cox, 1996). First, data were brain extracted (3dSkullStrip). Then, using afni_proc.py, TRs where the Euclidian Norm of the motion derivative exceeded 0.3mm were excluded from the analysis. Functional data were slice timing corrected (3dTshift), motion corrected (3dvolreg), and blurred to 2mm (3dmerge). Each subject's functional data was aligned to their anatomical scan (3dallineate). Then, we used ANTs (Advanced Normalization Techniques) software (Avants et al., 2009) to align each subject's data to a common template.

FMRI Analysis- Encoding

Event boundaries were entered into a GLM as a single regressor in addition to 6-dimensional motion regressors generated during motion correction, using AFNI's 3dDeconvolve function. Each participant's structural T1-weighted image was warped to

a template using ANTs. Those same warp parameters were then used to bring each participant's functional data into that same template space.

This analysis focused on the "event boundaries > baseline" contrast. Data from all subjects were tested against 0 using AFNI's 3dttest++ function and were thresholded at p = 0.05, cluster extent threshold = 1607 as indicated by AFNI's 3dClustSim function. We identified significant clusters in the superior temporal gyrus, indicating that this region is preferentially active at event boundaries (**Figure 14**). However, it is important to note that *Curb Your Enthusiasm* plays music at some event boundaries, which may contribute to the preferential superior temporal gyrus activation observed at event boundaries.

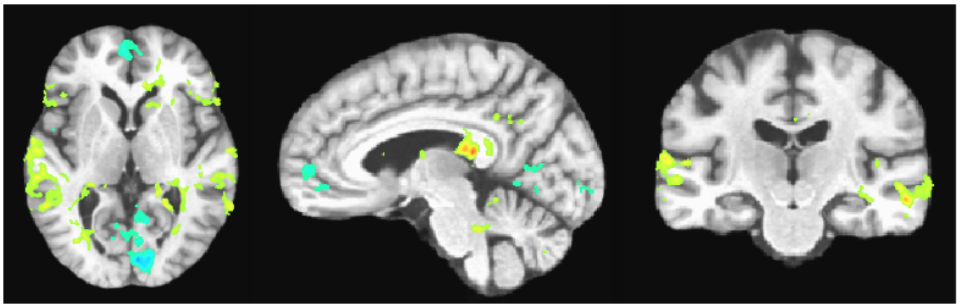
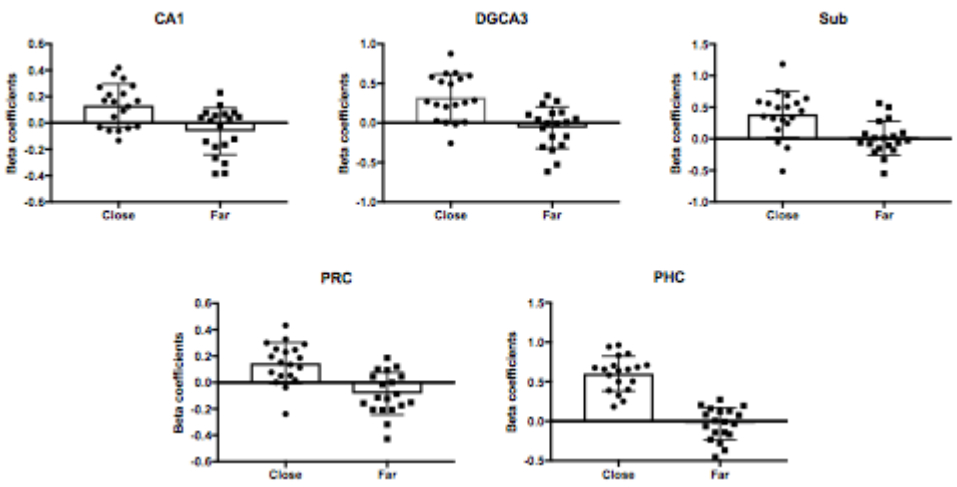


Figure 14: Clusters in the superior temporal gyrus were reliably activated at event boundaries (defined here as scene changes).



FMRI Analysis-Retrieval

Trials were sorted based on their

Figure 15: Regions showing significantly greater BOLD fMRI activity for trials closest to event boundaries compared to the trials that were the farthest away.

minimum distance from an event boundary. They were divided into thirds (close, medium, and far distance from event boundary) and those three regressors were entered into a GLM and were transformed into template space, as described above. We restricted our analysis to task-activated voxels which we obtained by thresholding the full F-statistic containing all experimental conditions (thresholded at p = 0.25, cluster extent threshold = 20), which thus does not bias voxel selection towards any particular condition of interest.

We found that all tested regions were significantly more active for trials with the shortest distance from event boundary, compared to those that were farthest away (**Figure 15**). This was true for hippocampal subfields DGCA3 (p=0.000006), CA1 (p=0.00008), and the subiculum (p=0.00002), as well as PHC (p=0.00000001) and PRC (p=0.00002), Bonferroni-Holm corrected.

Discussion

Our behavioral data show no effect of event boundaries on memory for timing information. Memory for when still frames occurred during the video was not significantly different whether they were viewed close to or far from a scene change. This was unexpected given the fact that asking participants to segment events improved memory performance (Flores et al., 2017) and cuing at event boundaries improves memory (D. A. Gold et al., 2017).

More specifically, prior event segmentation literature suggests memory may improve at event boundaries. After viewing a short film, participants has higher recognition performance for events near boundaries (Newtson & Engquist, 1976). When commercial breaks were placed at event boundaries in a video, participants had higher recognition memory performance (Boltz, 1992). Another study found that participants were better at remembering the color associated with objects when they were presented at event boundaries (Heusser et al., 2018).

However, it is important to consider how event boundaries are defined. The vast majority of event segmentation studies define an event as either a meaningful unit of activity (such as filling a pot with water, or putting the pot on the stove) or a change in a stream of objects being viewed (such as a change in category of the objects or some contextual feature). In the present work, the episode of *Curb Your Enthusiasm* does not contain many easily identifiable fine-grained events. Instead, for most of the episode the main action relates to the dialog between characters, as opposed to physical actions they take. As a result, the clearest and most objective event boundaries seem to be at scene changes. This difference may partially explain why we did not observe an effect of distance from event boundaries on memory performance.

Alternatively, it may be that event boundaries have different effects on memory for timing information as opposed to recognition memory. The most relevant studies have mainly tested the effect of proximity to boundaries on recognition memory (Boltz, 1992; Newtson & Engquist, 1976). Other studies explicitly testing temporal memory tested differences in memory within vs. across event boundaries (DuBrow & Davachi, 2016; Heusser et al., 2018), which was not possible in the current work.

Our fMRI results show increased activity of the STG at event boundaries. This fits well with prior work showing that several brain regions, including the STG, were preferentially activated at event boundaries while participants read narratives inside the MRI scanner (Speer et al., 2007). In the present study, it is important to note that *Curb Your Enthusiasm* uses distinctive music at some scene changes. This music could partially explain the preferential activity of STG at event boundaries that we observed, since the STG is involved in auditory processing (Rauschecker, 2013). It is also possible that STG plays a role in marking event boundaries, since it has been shown to be activated at boundaries when participants read silently in the MRI scanner. Future studies should be sure to decouple sound from event boundaries for more straightforward interpretation of results.

One limitation of this work is the way in which we defined event boundaries. In the current work, the closest even boundary is the closest boundary *either before or after* a

given still-frame appeared at encoding. However, it is likely that boundaries after a given still-frame have a bigger effect on cognitive processing. Trials where the closest boundary is after the still frame may be dominating the BOLD fMRI data, leading to the observed neural effects in the absence of a behavioral effect. Additionally, factors such as novelty and the changing of context present at boundaries may contribute to the observed effects in medial temporal lobe subregions.

Our analysis of retrieval data indicates that all MTL regions tested responded preferentially to trials that were closest to an event boundary. However, these results should be interpreted with caution since there was no behavioral effect of event boundary on memory performance. In light of this fact, it is difficult to interpret these results. It could be that the medial temporal lobe was sensitive to spatial/object/contextual changes at these boundaries, since MTL subregions have been implicated in spatial and object memory (Baumann, Chan, & Mattingley, 2010; H Eichenbaum & Lipton, 2008; Nadel, Hoscheidt, & Ryan, 2013; Ryan, Lin, Ketcham, & Nadel, 2010) and in novelty detection (Barbeau, Chauvel, Moulin, Regis, & Liégeois-Chauvel, 2017).

Overall, future work should use neuroimaging and behavioral tests to bridge the gap between the fields of memory for timing information and event segmentation. Several studies have shown that the act of marking event boundaries improves memory (Flores

et al., 2017; Sols, DuBrow, Davachi, & Fuentemilla, 2017), but the mechanisms of this effect remain unclear. Combining behavioral performance measures (temporal, recognition, and recall memory) with neuroimaging will help establish brain-behavior relationships that will explain how and under what circumstances event segmentation exerts its effects on memory.

CHAPTER 4: TEMPORAL MEMORY PRECISION IN OLDER ADULTS

Abstract

Memory for timing information is critical for understanding and learning from our experiences. For example, if we get sick, it is valuable to remember what was eaten soon before falling ill. However, it is not always possible to retrieve information about the sequence or timing of experiences. Prior work identified a network of regions that preferentially activated for trials with high memory precision for timing information (Montchal, Reagh, & Yassa, 2019). Using the same paradigm, we found that older adults performed similarly to young adults. We also found that older adults' error on the task correlated with the RAVLT-Delay neuropsychological test. Future work should investigate brain-behavior relationships by testing whether measures such as cortical thickness also correlate with performance in older adults.

Introduction

Memories are organized in time, but it can be difficult to remember when certain events occurred. Memory performance declines even in healthy aging (Davis et al., 2013; Harada et al., 2013; Isingrini & Taconnat, 2008). Some neural mechanisms associated with age-related memory decline have been identified. For example, some amount of grey matter volume loss and amyloid-beta deposition is considered normal in aging (Harada et al., 2013). White matter volume also decreases, notably in the parahippocampal region, which could impair the flow of information into the hippocampus (Rogalski et al., 2012; Stoub et al., 2012).

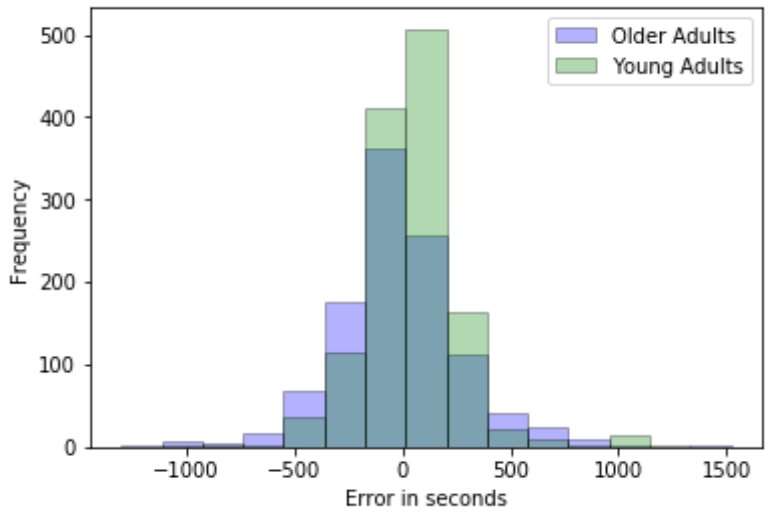


Figure 16: Behavioral performance on a task testing memory precision (error in seconds) for timing information for groups of older and young adults.

Temporal memory seems to be especially vulnerable to decline in aging. Older adults perform significantly worse than younger adults on tests of memory for timing information (Pirogovsky et al., 2013; Seewald et al., 2017). This is true even when there is no age-related difference in performance on recognition memory (Fabiani & Friedman, 2013).

Recent work has identified functional alterations in the entorhinal-hippocampal network in older adults (Reagh et al., 2018). Specifically, older adults who were impaired on an object discrimination memory task had hypoactivity in the anterolateral entorhinal cortex (aLEC) and hyperactivity in the dentate gyrus/CA3 region of the hippocampus (Reagh et al., 2018). The behavioral paradigm used in this study was previously used in healthy young adults. We found that increased aLEC activity was associated with high temporal memory precision. The goal of this study is to test whether older adults perform comparably to younger adults on this task and whether there is a relationship between performance and neurpsychological test scores.

Methods and Results

Task

Separate groups of older adults and young adults were shown an episode of *Curb Your Enthusiasm* and then answered questions about when still-frames during the episode occurred, as described in previous chapters. The version of the temporal memory test task taken by older adults was self-paced, while young adults had 9 seconds to move the cursor on each trial. All participants also underwent neuropsychological testing, including the Rey Auditory Verbal Learning Test (RAVLT) Delay and Mini-Mental State Exam (MMSE).

Behavioral Analysis

In each age group, we excluded participants who scored +/- two standard deviations from the mean in RAVLT Delay, MMSE, or average error on the temporal precision task. This left us with 18 younger adults and 15 older adults for the subsequent analyses. For older adults, the mean error value (distance in seconds between the participant's response and when a still-frame actually happened) was 211.75 seconds, and the median was 215.5833 seconds, with a standard deviation of 58.6654 seconds. The mean error value for young adults was 158.2768, the median was 154.6806 seconds, and the standard deviation was 39.9575 seconds.

Next, we tested whether older and young adult performance on the task was significantly different. A Kolmogorov-Smirnov test found no significant difference between the two groups (K-S D=0.4667, p=0.0567), indicating that older and young adults had comparable error rates on the task.

Next, we wanted to investigate whether RAVLT-Delay scores and age were related to performance on this task. We excluded MMSE scores from further analysis due to low variability of scores in both groups (Older adults SD=1.534, minimum=25, maximum=30, mean=28.07; young adults SD=0.8782, minimum=26, maximum=30, mean=28.22).

We ran a partial correlation on our cohort of young adults, testing for a relationship between error on the task and RAVLT Delay score, controlling for age (using the ppcor library in R). We found no significant correlation (Pearson partial correlation coefficient = 0.0608, test statistic = 0.2359, p = 0.8167), indicating there is not a detectable linear relationship between task performance and RAVLT Delay score in young adults.

We ran the same partial correlation in older adults and found a significant negative correlation between error on the task and RAVLT Delay scores in older adults, while controlling for age (Pearson partial correlation coefficient = -0.618, test statistic = -2.7232, p = 0.0185). This indicates that, on average, higher RAVLT Delay scores are associated with lower error on the temporal precision memory task, in older adults.

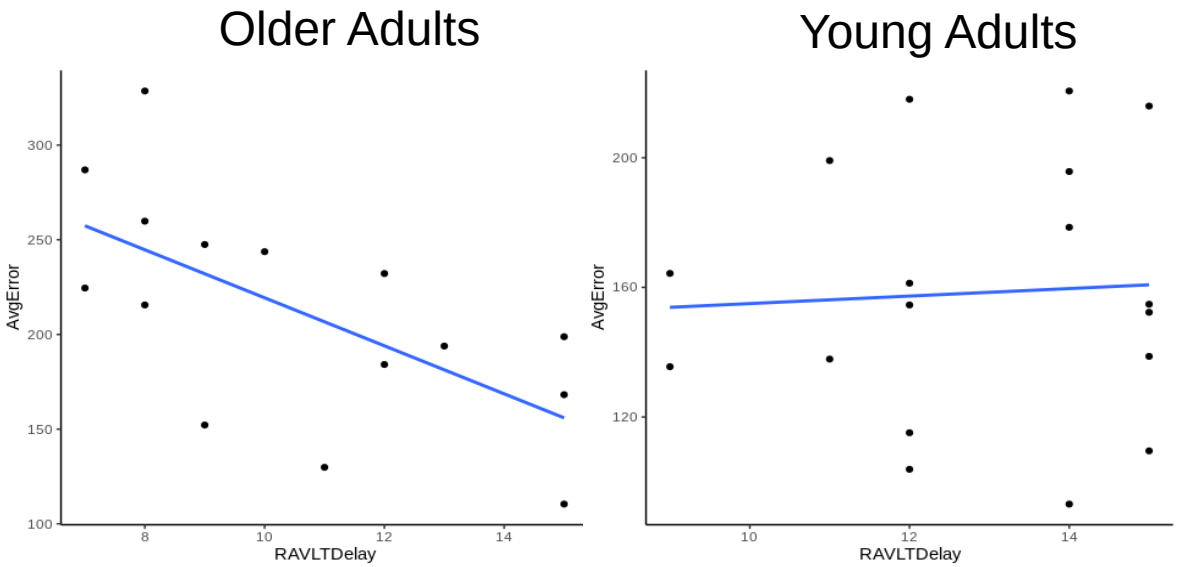


Figure 17: Association between error on the task and RAVLT-Delay performance, plotted with trendline. We found a significant partial correlation between error on the task in older adults (Pearson partial correlation coefficient=-0.618, p=0.0185) but not young adults (Pearson partial correlation coefficient=0.0608, p=0.8167).

Discussion

We predicted that older adults would have significantly higher error on the temporal precision memory task, compared to younger adults, but we found no difference. One factor that may have led to these results is that we gave older adults more time to complete the task. Young adults had 9 seconds on each trial to indicate when they thought each still frame had occurred during the video. Because older adults are typically less familiar with using a mouse and especially the scroll wheel of the mouse which is necessary for this task, we gave older adults as much time as they needed. The task was self-paced in older adults, and they pressed the space bar when they were satisfied with their response.

Another possible factor is that we currently have a relatively small sample size. Since the p-value for the K-S test is nearly significant, it's possible that increasing the sample size to 25 in each group could result in a significant difference between older and young adult performance. However, even if older and young adult performance is similar, it is still possible to find important differences in other measures as they relate to performance. For example, if cortical thickness in a region correlates with task performance in older but not young adults, this could give us important information about brain changes in aging.

One strength of this study is that it is more likely to generalize to memory for events in an older adult's life than studies involving object sequence memory. We used an episode of *Curb Your Enthusiasm* in this study in an effort to bring more life-like situations into the laboratory. The video involved sight, sound, and was more likely to evoke common emotional responses like annoyance or amusement than typical tests of temporal memory.

We also found a relationship between performance in this same task and the RAVLT in older, but not young, adults. The RAVLT is sensitive to early age-related memory impairments. RAVLT scores can be used to predict participants at high and low risk of cognitive decline (Andersson et al., 2006). Since the current task results in an average error value for each participant-- that is, their average distance in seconds from when

each still-frame occurred during the video, this task may also be helpful in predicting risk of cognitive decline. Future work should explore whether neuroimaging data, such as cortical thickness measures or patterns of functional connectivity, can explain variance in behavioral performance. It may be possible to leverage the decline in temporal memory performance with aging to detect preclinical memory impairments.

CHAPTER: CONCLUSIONS AND FUTURE DIRECTIONS

General Summary and Current State of Knowledge

Humans often find it difficult to remember when events occurred, even if they can remember the event itself. There is relatively little known about memory for timing information, compared to spatial information. Existing studies have provided evidence that the hippocampus and other medial temporal lobe regions work together to support memory for timing information.

Many gaps in our knowledge about memory for timing information still exist. Most research in this field has focused on memory for sequences of static objects (or typically odors, in rodents). These sequences can span a few seconds. Time cells identified in the hippocampus respond at reliable timepoints during a delay between trials, which also last a few seconds (MacDonald et al., 2011). Other work has found that patterns of hippocampal activity grow more dissimilar over several hours (Mankin et al., 2012), providing support for the Temporal Context Model (Howard & Kahana, 2002).

It remains unclear how the brain, and the hippocampus in particular, move from stable time fields on the order of seconds to a gradually evolving temporal context on the order of hours or days. A recent study made a significant contribution to this question, by showing time-related firing for periods spanning seconds, minutes, and hours (Mau et al., 2018). They found that some hippocampal “time fields” on the order of seconds dropped out before hours elapsed, but that this did not disrupt the evolving temporal context. That is, they were still able to decode the passage of time for periods of hours based on hippocampal CA1 activity.

The hippocampus plays an important role in memory for time, but it does not act alone. As the field gains a greater understanding of how the hippocampus tracks time on a neuronal/ensemble level, questions remain about how timing information is maintained and processed both before and after it reaches the hippocampus. One major goal of this dissertation was to identify brain regions that support the retrieval of precise memories for when events occurred in a situation comedy. We also tested the role of event boundaries in memory for time, as well as whether temporal memory precision declines in aging.

Temporal Memory in Healthy Young Adults

We developed and implemented a more naturalistic task testing memory for timing information in healthy young adults. In this experiment, participants viewed an episode of a situation comedy, *Curb Your Enthusiasm*, and later indicated when during the episode they thought still frames occurred. This allowed us to measure their precision for each trial (the distance in seconds between when they thought each still frame occurred and when it actually occurred during the episode). We found a network of regions, including the hippocampus, LEC, and PRC (but not PHC or MEC), were preferentially active for the most temporally precise trials (where participants were closest to the correct answer when indicating when a still-frame occurred).

These results are somewhat surprising in light of previous studies showing a role for PHC and, possibly by nature of their anatomical connectivity, pMEC in spatial memory. A few studies have even implicated PHC in memory for time (Hsieh et al., 2014; Jenkins & Ranganath, 2010; Lehn et al., 2009). Discussing this work in the context of prior studies is complicated by the fact that researchers may not have looked for temporal memory effects in PRC/LEC and may not have reported them even if they did exist.

The work described in this dissertation also differs in several ways from these previous studies, which could explain the divergent results. First, it tested memory for time over the course of the ~30 minute situation comedy episode. This is considerably longer than the stream of 5-10 object sequences, which typically takes under a minute to present.

Second, in contrast with well-learned object sequences, the episode was only viewed once. Third, the episode involves many more senses (audition, watching characters move in space, it may evoke emotion like amusement or annoyance) than traditional laboratory tests of temporal memory. Any of these factors could contribute to the surprising finding of PRC/LEC, not PHC/MEC preferentially activating for trials with the highest temporal precision.

Moreover, the results presented in this dissertation are partially consistent with a recent study investigating memory for time in the LEC. Researchers were able to decode timing information from freely behaving rats through ensemble activity in the LEC (Tsao et al., 2018). The authors suggest that timing information from LEC may be integrated with spatial information from MEC in the hippocampus. Recent fMRI work was able to decode conjunctive item and temporal information from the hippocampus, but not temporal information alone. It is possible that the LEC may be an important part of the temporal memory network, and it may work together with other medial temporal lobe and striatal regions to integrate timing information into memory.

Event Segmentation in Memory for Time

Using the same paradigm described above, we identified event boundaries as scene changes during the episode of *Curb Your Enthusiasm*. We found no evidence that event boundaries affect temporal memory precision in this task. Despite the lack of behavioral

effect, we tested whether medial temporal lobe subregions were differentially sensitive to event boundaries. We found that all a priori regions tested, including hippocampal subfields (CA1, DG/CA3, and the subiculum) as well as PRC/PHC were significantly more active for trials closest to event boundaries.

We also identified a cluster in the STG that was significantly activated at event boundaries. This is consistent with previous work that found STG activation at event boundaries when participants read a narrative text in the MRI scanner (Speer et al., 2007). However, *Curb Your Enthusiasm* plays music at some scene changes, which may partially explain this finding, since the STG is involved in audition.

Temporal Memory in Older Adults

We tested healthy older adults on the same task taxing memory for time. We found that they performed significantly worse than younger adults. We also found that RAVLT-Delay performance explained a significant amount of the variance in task performance. This indicates that performance on the temporal precision task may be tapping into memory processes that are measured by neuropsychological tests, like the RAVLT-Delay. Since this task seems to be sensitive to age-related memory changes, it would be useful to test brain-behavior relationships in older adults.

Future Directions

Exciting new work involving more naturalistic stimuli has provided insights into event segmentation and memory processes (Baldassano et al., 2017; Lositsky, Chen, Toker, Honey, Shvartsman, et al., 2016). Future work in this vein will guide the interpretation of both naturalistic and traditional laboratory experiments, which is critical. This will allow the field to benefit from the strengths of each paradigm type. Currently, it is unclear whether or how memory for short events might differ from longer events than span hours or days. Testing the effect of event duration and whether there are effects on brain regions recruited will be an important finding that may come from this line of research. It will also be important to replicate these findings in both humans and non-human animals before any conclusive models of memory based on this work can be confidently formed.

One potential method to test interactions of different brain regions (such as PRC/LEC/the hippocampus) in memory for time is intracranial EEG in humans. This would allow for testing memory for time in a complex naturalistic task (such as video watching) with greater temporal resolution than fMRI allows. Depending on the location of electrodes in patients, this technique could be used to test the hypothesis that timing information enters the hippocampus through LEC, where it is bound to other relevant information (spatial, or internal state).

Another important issue to tackle is how timing information from the rest of the brain (such as the striatum) is combined with timing information in the hippocampus and integrated into memory. We don't currently understand the relative contributions of temporal landmarks (events we know occurred at a certain time) and internally generated clocking information. One way to investigate this would be to ask participants to use one of two strategies: answer when they "feel" like an event occurred, without thinking about the timing of other events, and 2) responding based on when they think the event occurred, based on temporal landmarks. We could then look at relative accuracy and brain regions which are more active in either condition.

An interesting next step is to test whether performance correlates with structural MRI measures, such as cortical thickness. Specifically, if thickness or volume of regions implicated in temporal precision in young adults, such as the hippocampus, LEC, and PRC correlated with task performance, that would provide a compelling link between structure and function of these regions. It could potentially provide more predictive information for cognitive aging than structural MRI can currently provide alone. Activity of MTL subregions may also be altered in aging, as shown by Reagh, Watabe, Ly, Murray, and Yassa, (2014). Overall activity or correlations of activity (functional connectivity) could be tested to see if they correlate with task performance. From this, it may be possible to determine patterns of activity that are associated with high or low performance on the temporal precision task. This could eventually lead to better, earlier

predictors of cognitive decline, which could make potential treatments more effective than they would be at a later stage.

Concluding Remarks

Overall, the work described in this dissertation contributes to knowledge about human memory for timing information. Chapter 2 revealed the neurobiological correlates of temporal precision memory. It lays the groundwork for future naturalistic studies of memory, by demonstrating that memory can be quantified and important variables can be controlled even with continuous, vivid stimuli (such as a video). Chapter 3 provided evidence that event boundaries do not significantly impact memory performance on this task. Future work should test whether this is true for other definitions of "events" that may be more fine-grained (such as shorter physical actions or shifts in goals) which were not abundant in this episode. Chapter 4 found that older adults performed no differently than young adults on this test of the precision of memory for time and proposed several potential factors that could have contributed to this finding and should be investigated in future research. Further work on temporal memory involving more real life-like paradigms will provide important information on the factors that affect brain networks that support temporal memory.

REFERENCES

Aggleton, J. P., & Brown, M. W. (1999). Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. *Behavioral and Brain Sciences*, *22*(3), 425–444. https://doi.org/10.1017/S0140525X99002034

Aggleton, J. P., Kyd, R. J., & Bilkey, D. K. (2004). When is the perirhinal cortex necessary for the performance of spatial memory tasks? *Neuroscience and Biobehavioral Reviews*, *28*(6), 611–624. https://doi.org/10.1016/j.neubiorev.2004.08.007

Aminoff, E., Kveraga, K., & Bar, M. (2013). The role of the parahippocampal cortex in cognition. *Trends Cogn Sci.*, *17*(8), 379–390. https://doi.org/10.1038/mp.2011.182.doi

Andersen, P., Bliss, T. V. P., & Skrede, K. K. (1971). Lamellar organization of hippocampal excitatory pathways. *Experimental Brain Research*, *13*(2), 222–238. https://doi.org/10.1007/BF00234087

Andersson, C., Lindau, M., Almkvist, O., Engfeldt, P., Johansson, S. E., & Jönhagen, M. E. (2006). Identifying patients at high and low risk of cognitive decline using Rey Auditory Verbal Learning Test among middle-aged memory clinic outpatients. *Dementia and Geriatric Cognitive Disorders*, *21*(4), 251–259. https://doi.org/10.1159/000091398

Avants, B. B., Tustison, N., & Song, G. (2009). Advanced Normalization Tools (ANTS). *Insight Journal*, 1–35. Retrieved from ftp://ftp3.ie.freebsd.org/pub/sourceforge/a/project/ad/advants/Documentation/ants.pdf

Baldassano, C., Chen, J., Zadbood, A., Pillow, J. W., Hasson, U., & Norman, K. A. (2017). Discovering Event Structure in Continuous Narrative Perception and Memory. *Neuron*, *95*(3), 709–721.e5. https://doi.org/10.1016/j.neuron.2017.06.041

Baldassano, C., Chen, J., Zadbood, A., Pillow, J. W., & Norman, K. A. (2018). and memory, *95*(3), 709–721. https://doi.org/10.1016/j.neuron.2017.06.041.Discovering

Barbeau, E. J., Chauvel, P., Moulin, C. J. A., Regis, J., & Liégeois-Chauvel, C. (2017). Hippocampus duality: Memory and novelty detection are subserved by distinct mechanisms. *Hippocampus*, *27*(4), 405–416. https://doi.org/10.1002/hipo.22699

Baumann, O., Chan, E., & Mattingley, J. B. (2010). Dissociable neural circuits for encoding and retrieval of object locations during active navigation in humans. *NeuroImage*, *49*(3), 2816–2825. https://doi.org/10.1016/j.neuroimage.2009.10.021

Bellmund, J. L. S., Deuker, L., & Doeller, C. F. (2019). Structuring Time in Human Lateral Entorhinal Cortex. *BioRxiv*, 458133. https://doi.org/10.1101/458133

Ben-Yakov, A., & Henson, R. N. (2018). The Hippocampal Film Editor: Sensitivity and Specificity to Event Boundaries in Continuous Experience. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *38*(47), 10057–10068. https://doi.org/10.1523/JNEUROSCI.0524-18.2018

Bohbot, V. D., Allen, J. J. B., Dagher, A., Dumoulin, S. O., Evans, A. C., Petrides, M., … Nadel, L. (2015). Role of the parahippocampal cortex in memory for the configuration but not the identity of objects: converging evidence from patients with selective thermal lesions and fMRI. *Frontiers in Human Neuroscience*, *9*(August), 1–17. https://doi.org/10.3389/fnhum.2015.00431

Boltz, M. (1992). Temporal Accent Structure and the Remembering of Filmed Narratives. *Journal of Experimental Psychology: Human Perception and Performance*, *18*(1), 90–105. https://doi.org/10.1037/0096-1523.18.1.90

Brun, V. H., Solstad, T., Kjelstrup, K. B., Fyhn, M., Witter, M. P., Moser, E. I., & Moser, M.-B. (2008). Progressive increase in grid scale from dorsal to ventral medial entorhinal cortex. *Hippocampus*, *18*(12), 1200–1212. https://doi.org/10.1002/hipo.20504

Buckley, M. J., & Gaffan, D. (2000). *The hippocampus, perirhinal cortex and memory in the monkey.* https://doi.org/10.1093/acprof

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

Buhusi, C. V, & Meck, W. H. (2005). What makes us tick? Functional and neural mechanisms of interval timing. *Nature Reviews. Neuroscience*, *6*(10), 755–765. https://doi.org/10.1038/nrn1764

Burwell, R. D., & Amaral, D. G. (1998). Perirhinal and postrhinal cortices of the rat: Interconnectivity and connections with the entorhinal cortex. *Journal of Comparative Neurology*, *391*(3), 293–321. https://doi.org/10.1002/(SICI)1096-9861(19980216)391:3<293::AID-CNE2>3.0.CO;2-X

Bussey, T. J., Duck, J., Muir, J. L., & Aggleton, J. P. (2000). Distinct patterns of behavioural impairments resulting from fornix transection or neurotoxic lesions of the perirhinal and postrhinal cortices in the rat. *Behavioural Brain Research*, *111*(1–2), 187–202. https://doi.org/10.1016/S0166-4328(00)00155-8

Cabeza, R., Prince, S. E., Daselaar, S. M., Greenberg, D. L., Budde, M., Dolcos, F., … Rubin, D. C. (2004). Brain Activity during Episodic Retrieval of Autobiographical and Laboratory Events: An fMRI Study using a Novel Photo Paradigm. *Journal of Cognitive Neuroscience*, *16*(9), 1583–1594. https://doi.org/10.1162/0898929042568578

Chadwick, M. J., Hassabis, D., Weiskopf, N., & Maguire, E. A. (2010). Decoding Individual Episodic Memory Traces in the Human Hippocampus. *Current Biology*, *20*(6), 544–547. https://doi.org/10.1016/j.cub.2010.01.053

Chen, J., Honey, C. J., Simony, E., Arcaro, M. J., Norman, K. A., & Hasson, U. (2016). Accessing Real-Life Episodic Information from Minutes versus Hours Earlier Modulates Hippocampal and High-Order Cortical Dynamics. *Cerebral Cortex*, *26*(8), 3428–3441. https://doi.org/10.1093/cercor/bhv155

Clayton, N. S., & Dickinson, a. (1998). Episodic-like memory during cache recovery by scrub jays. *Nature*, *395*(6699), 272–274. https://doi.org/10.1038/26216

Clewett, D., & Davachi, L. (2017). The Ebb and Flow of Experience Determines the Temporal Structure of Memory. *Curr Opin Behav Sci*, *17*, 186–193. https://doi.org/10.1037/h0076782

Cohen, N. J., & Squire, L. R. (1980). Preserved Learning and Retention of Pattern-Analyzing Skill in Amnesia : Dissociation of Knowing How and Knowing that Author (s): Neal J . Cohen and Larry R . Squire. *Science*, *210*(4466), 207–210.

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research*, *29*(29), 162–173. https://doi.org/10.1006/cbmr.1996.0014

Davis, H. P., Klebe, K. J., Guinther, P. M., Schroder, K. B., Cornwell, R. E., & James, L. E. (2013). Subjective organization, verbal learning, and forgetting across the life Span: From 5 to 89. *Experimental Aging Research*, *39*(1), 1–26. https://doi.org/10.1080/0361073X.2013.741956

Deshmukh, S. S., & Knierim, J. J. (2011). Representation of Non-Spatial and Spatial Information in the Lateral Entorhinal Cortex. *Frontiers in Behavioral Neuroscience*, *5*(October). https://doi.org/10.3389/fnbeh.2011.00069

Devito, L. M., & Eichenbaum, H. (2011). Memory for the order of events in specific sequences: contributions of the hippocampus and medial prefrontal cortex. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *31*(9), 3169–3175. https://doi.org/10.1523/JNEUROSCI.4202-10.2011

Diehl, G. W., Hon, O. J., Leutgeb, S., Leutgeb, J. K., Diehl, G. W., Hon, O. J., … Leutgeb, J. K. (2017). Grid and Nongrid Cells in Medial Entorhinal Cortex Represent Spatial Location and Environmental Features with Complementary Coding Schemes Report Grid and Nongrid Cells in Medial Entorhinal Cortex Represent Spatial Location and Environmental Features with. *Neuron*, *94*(1), 1–10. https://doi.org/10.1016/j.neuron.2017.03.004

Doron, A., & Goshen, I. (2017). Investigating the transition from recent to remote memory using advanced tools. *Brain Research Bulletin*, (July), 0–1. https://doi.org/10.1016/j.brainresbull.2017.09.005

DuBrow, S., & Davachi, L. (2016). Temporal binding within and across events. *Neurobiology of Learning and Memory*. https://doi.org/10.1016/j.nlm.2016.07.011

Dumas, J. A., & Hartman, M. (2003). Adult age differences in temporal and item memory. *Psychology and Aging*, *18*(3), 573–586. https://doi.org/10.1037/0882-7974.18.3.573

Eichenbaum, H. (2017). On the Integration of Space, Time, and Memory. *Neuron*, *95*(5), 1007–1018. https://doi.org/10.1016/j.neuron.2017.06.036

Eichenbaum, H., & Lipton, P. a. (2008). Towards a functional organization of the meidal temporal lobe memory system: Role of the parahippocampal and medial entorhinal areas. *Hippocampus*, *18*(12), 1314–1324. https://doi.org/10.1002/hipo.20500.Towards

Eichenbaum, H., Yonelinas, A. P., & Ranganath, C. (2007). The medial temporal lobe and recognition memory. *Annual Reviews of Neuroscience*, *30*, 123–152. https://doi.org/10.1146/annurev.neuro.30.051606.094328

Ekstrom, A. D., & Bookheimer, S. Y. S. (2007). Spatial and temporal episodic memory retrieval recruit dissociable functional networks in the human brain. *Learning & Memory*, *14*(10), 645–654. https://doi.org/10.1101/lm.575107.Several

Ekstrom, A. D., & Ranganath, C. (n.d.). Space , Time and Episodic Memory : the Hippocampus is all over the Cognitive Map CA , USA 2 . Department of Psychology , University of California , Davis , CA , USA 3 . Neuroscience Graduate Group , University of California , Davis , CA , USA * Each autho, 1–16.

El Haj, M., & Kapogiannis, D. (2016). Time distortions in Alzheimer's disease: a systematic review and theoretical integration. *Aging and Mechanisms of Disease*, *2*(April), 16016. https://doi.org/10.1038/npjamd.2016.16

Epstein, R. A., Parker, W. E., & Feiler, A. M. (2007). Where Am I Now? Distinct Roles for Parahippocampal and Retrosplenial Cortices in Place Recognition. *Journal of Neuroscience*, *27*(23), 6141–6149. https://doi.org/10.1523/JNEUROSCI.0799-07.2007

Ergorul, C., & Eichenbaum, H. (2004). The hippocampus and memory for [ldquo]what, [rdquo] [ldquo]where,[rdquo] and [ldquo]when.[rdquo]. *Learn. Mem.*, *11*(13), 397–405. https://doi.org/10.1101/lm.73304.mals

Fabiani, M., & Friedman, D. (1997). Dissocciations between memory for temporal order and recognition memory in aging. *Neuropsychologia*, *35*(2), 129–141.

Fink, G. R., Markowitsch, H. J., Reinkemeier, M., Bruckbauer, T., Kessler, J., & Heiss, W.-D. (1996). Cerebral Representation of One's Own Past: Neural Networks Involved in Autobiographical Memory. *The Journal of Neuroscience*, *16*(13), 4275–4282. https://doi.org/10.1523/jneurosci.16-13-04275.1996

Flores, S., Bailey, H. R., Eisenberg, M. L., & Zacks, J. M. (2017). Event segmentation improves event memory up to one month later. *Journal of Experimental Psychology: Learning Memory and Cognition*, *43*(8), 1183–1202. https://doi.org/10.1037/xlm0000367

Fontes, R., Ribeiro, J., Gupta, D. S., Machado, D., Lopes-Júnior, F., Magalhães, F., … Teixeira, S. (2016). Time perception mechanisms at central nervous system. *Neurology International*, *8*(1). https://doi.org/10.4081/ni.2016.5939

Furman, O., Dorfman, N., Hasson, U., Davachi, L., & Dudai, Y. (2007). They saw a movie: Long-term memory for an extended audiovisual narrative. *Learning & Memory*, *14*(6), 457–467. https://doi.org/10.1101/lm.550407

Gilboa, A. (2004). Autobiographical and episodic memory - One and the same? Evidence from prefrontal activation in neuroimaging studies. *Neuropsychologia*, *42*(10), 1336–1349. https://doi.org/10.1016/j.neuropsychologia.2004.02.014

Glover, G. H. (2011). Overview of functional magnetic resonance imaging. *Neurosurgery Clinics of North America*, *22*(2), 133–139. https://doi.org/10.1016/j.nec.2010.11.001

Gold, A. E., & Kesner, R. P. (2005). The role of the CA3 subregion of the dorsal hippocampus in spatial pattern completion in the rat. *Hippocampus*, *15*(6), 808–814. https://doi.org/10.1002/hipo.20103

Gold, D. A., Zacks, J. M., & Flores, S. (2017). Effects of cues to event segmentation on subsequent memory. *Cognitive Research: Principles and Implications*, *2*(1), 1–15. https://doi.org/10.1186/s41235-016-0043-2

Gould, T. J., Rowe, W. B., Heman, K. L., Mesches, M. H., Young, D. A., Rose, G. M., & Bickford, P. C. (2002). Effects of hippocampal lesions on patterned motor learning in the rat. *Brain Research Bulletin*, *58*(6), 581–586. https://doi.org/10.1016/S0361-9230(02)00832-8

Hafting, T., Fyhn, M., Molden, S., Moser, M. B., & Moser, E. I. (2005). Microstructure of a spatial map in the entorhinal cortex. *Nature*, *436*(7052), 801–806. https://doi.org/10.1038/nature03721

Hannesson, D. K. (2004). Interaction between Perirhinal and Medial Prefrontal Cortex Is Required for Temporal Order But Not Recognition Memory for Objects in Rats.

Journal of Neuroscience, *24*(19), 4596–4604. https://doi.org/10.1523/JNEUROSCI.5517-03.2004

Harada, C. N., Love, M. C. N., & Triebel, K. (2013). Normal Cognitive Aging. *Clin Geriatr Med.*, *29*(4), 737–752. https://doi.org/10.1016/j.cger.2013.07.002.Normal

Hartley, T., Lever, C., Burgess, N., & O'Keefe, J. (2013). Space in the brain: how the hippocampal formation supports spatial cognition. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *369*(1635), 20120510–20120510. https://doi.org/10.1098/rstb.2012.0510

Hasselmo, M. E. (2005). 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). *Behavioral Neuroscience*, *119*(1), 342–345. https://doi.org/10.1037/0735-7044.119.1.342

Hasson, U., Landesman, O., Knappmeyer, B., Vallines, I., Rubin, N., & Heeger, D. J. (2008). Neurocinematics : The Neuroscience of Film, *2*(1), 1–26.

Heusser, A., Ezzyat, Y., Schiff, I., & Davachi, L. (2018). Perceptual boundaries cause mnemonic trade-offs between local boundary processing and across-trial associative binding, *44*(7), 1075–1090. https://doi.org/10.1002/cncr.27633.Percutaneous

Howard, M. W., & Kahana, M. J. (2002). A Distributed Representation of Temporal Context. *Journal of Mathematical Psychology*, *46*(3), 269–299. https://doi.org/10.1006/jmps.2001.1388

Howard, M. W., Viskontas, I. V., Shankar, K. H., & Fried, I. (2012). Ensembles of human MTL neurons "jump back in time" in response to a repeated stimulus. *Hippocampus*, *22*(9), 1833–1847. https://doi.org/10.1002/hipo.22018

Hsieh, L. T., Gruber, M. J., Jenkins, L. J., & Ranganath, C. (2014). Hippocampal Activity Patterns Carry Information about Objects in Temporal Context. *Neuron*, *81*(5), 1165–1178. https://doi.org/10.1016/j.neuron.2014.01.015

Hut, R. A., & Van der Zee, E. A. (2011). The cholinergic system, circadian rhythmicity, and time memory. *Behavioural Brain Research*, *221*(2), 466–480. https://doi.org/10.1016/j.bbr.2010.11.039

Hymel, A., Levin, D. T., & Baker, L. J. (2016). Default processing of event sequences. *Journal of Experimental Psychology: Human Perception and Performance*, *42*(2), 235–246. https://doi.org/10.1037/xhp0000082

Insausti, R., Herrero, M. T., & Witter, M. P. (1997). Entorhinal cortex of the rat: Cytoarchitectonic subdivisions and the origin and distribution of cortical efferents. *Hippocampus*, *7*(2), 146–183. https://doi.org/10.1002/(SICI)1098-1063(1997)7:2<146::AID-HIPO4>3.0.CO;2-L

Isingrini, M., & Taconnat, L. (2008). Mémoire épisodique, fonctionnement frontal et vieillissement. *Revue Neurologique*, *164*(SUPPL. 3). https://doi.org/10.1016/S0035-3787(08)73297-1

Jacobs, N. S., Allen, T. a, Nguyen, N., & Fortin, N. J. (2013). Critical role of the hippocampus in memory for elapsed time. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *33*(34), 13888–13893. https://doi.org/10.1523/JNEUROSCI.1733-13.2013

Jenkins, L. J., & Ranganath, C. (2010). Prefrontal and medial temporal lobe activity at encoding predicts temporal context memory. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *30*(46), 15558–15565. https://doi.org/10.1523/JNEUROSCI.1337-10.2010

Jeunehomme, O., & D'Argembeau, A. (2018). Event segmentation and the temporal compression of experience in episodic memory. *Psychological Research*, *0*(0), 1–10. https://doi.org/10.1007/s00426-018-1047-y

Jung, M. W., Wiener, S. I., & McNaughton, B. L. (1994). Comparison of spatial firing characteristics of units in dorsal and ventral hippocampus of the rat. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *14*(12), 7347–7356.

Keene, C. S., Bladon, J., McKenzie, S., Liu, C. D., Keefe, J. O., & Eichenbaum, H. (2016). Complementary Functional Organization of Neuronal Activity Patterns in the Perirhinal , Lateral Entorhinal , and Medial Entorhinal Cortices. *Journal of Neuroscience*, *36*(13), 3660–3675. https://doi.org/10.1523/JNEUROSCI.4368-15.2016

Kesner, R., Gilbert, P., & Barua, L. (2002). The role of the hippocampus in memory for the temporal order of a sequence of odors. *Behav Neurosci*, *116*(2), 286–290.

Kesner, R. P., & Hunsaker, M. R. (2010). The temporal attributes of episodic memory. *Behavioural Brain Research*, *215*(2), 299–309. https://doi.org/10.1016/j.bbr.2009.12.029

Kim, H., & Cabeza, R. (2007). Trusting our memories: Dissociating the neural correlates of confidence in veridical versus illusory memories. *Journal of Neuroscience*, *27*(45), 12190–12197. https://doi.org/10.1523/JNEUROSCI.3408-07.2007

Knierim, J. J., Neunuebel, J. P., Deshmukh, S. S., & Knierim, J. J. (2014). Functional correlates of the lateral and medial entorhinal cortex : objects , path integration and local – global reference frames.

Kraus, B. J., Brandon, M. P., Robinson, R. J., Connerney, M. A., Hasselmo, M. E., & Eichenbaum, H. (2015). During Running in Place, Grid Cells Integrate Elapsed Time and Distance Run. *Neuron*, *88*(3), 578–589. https://doi.org/10.1016/j.neuron.2015.09.031

Kraus, B. J., Robinson, R. J., White, J. a, Eichenbaum, H., & Hasselmo, M. E. (2013). Hippocampal “Time Cells”: Time versus Path Integration. *Neuron*, *78*(6), 1090–1101. https://doi.org/10.1016/j.neuron.2013.04.015

Krumm, S., Kivisaari, S. L., Probst, A., Monsch, A. U., Reinhardt, J., Ulmer, S., … Taylor, K. I. (2016). Cortical thinning of parahippocampal subregions in very early Alzheimer’s disease. *Neurobiology of Aging*, *38*, 188–196. https://doi.org/10.1016/j.neurobiolaging.2015.11.001

Kumaran, D., & Maguire, E. a. (2009). Novelty signals: a window into hippocampal information processing. *Trends in Cognitive Sciences*, *13*(2), 47–54. https://doi.org/10.1016/j.tics.2008.11.004

Kwok, S. C., & Macaluso, E. (2015a). Immediate memory for “when, where and what”: Short-delay retrieval using dynamic naturalistic material. *Human Brain Mapping*, *36*(7), 2495–2513. https://doi.org/10.1002/hbm.22787

Kwok, S. C., & Macaluso, E. (2015b). Scale invariance of temporal order discrimination using complex, naturalistic events. *Cognition*, *140*, 111–121. https://doi.org/10.1016/j.cognition.2015.04.007

Lavenex, P., & Amaral, D. G. (2000). Hippocampal-neocortical interaction: A hierarchy of associativity. *Hippocampus*, *10*(4), 420–430. https://doi.org/10.1002/1098-1063(2000)10:4<420::AID-HIPO8>3.0.CO;2-5

Lehn, H., Steffenach, H.-A., van Strien, N. M., Veltman, D. J., Witter, M. P., & Haberg, A. K. (2009). A Specific Role of the Human Hippocampus in Recall of Temporal Sequences. *Journal of Neuroscience*, *29*(11), 3475–3484. https://doi.org/10.1523/JNEUROSCI.5370-08.2009

Lindquist, M. a, & Wager, T. D. (2014). Principles of functional Magnetic Resonance Imaging. *Handbook of Neuroimaging Data Analysis*, 3–48.

Lisman, J. E., & Grace, A. a. (2005). The hippocampal-VTA loop: controlling the entry of information into long-term memory. *Neuron*, *46*(5), 703–713. https://doi.org/10.1016/j.neuron.2005.05.002

Liu, P., & Bilkey, D. K. (2002). The effects of NMDA lesions centered on the postrhinal cortex on spatial memory tasks in the rat. *Behavioral Neuroscience*, *116*(5), 860–873. https://doi.org/10.1037/0735-7044.116.5.860

Logothetis, N. K. (2002). The neural basis of the blood-oxygen-level-dependent functional magnetic resonance imaging signal. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *357*(1424), 1003–1037. https://doi.org/10.1098/rstb.2002.1114

Lositsky, O., Chen, J., Toker, D., Honey, C. J., Poppenk, J. L., Hasson, U., & Norman, K. A. (2016). Neural Pattern Change During Encoding of a Narrative Predicts Retrospective Duration Estimates. *BioRxiv*, 043075. https://doi.org/10.1101/043075

Lositsky, O., Chen, J., Toker, D., Honey, C. J., Shvartsman, M., Poppenk, J. L., … Norman, K. A. (2016). Neural pattern change during encoding of a narrative predicts retrospective duration estimates. *ELife*, *5*(NOVEMBER2016), 1–40. https://doi.org/10.7554/eLife.16070

Maass, A., Berron, D., Libby, L. A., Ranganath, C., & Düzel, E. (2015). Functional subregions of the human entorhinal cortex. *ELife*, *4*(JUNE), 1–20. https://doi.org/10.7554/eLife.06426

MacDonald, C. J., Carrow, S., Place, R., & Eichenbaum, H. (2013). Distinct hippocampal time cell sequences represent odor memories in immobilized rats.

The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, *33*(36), 14607–14616. https://doi.org/10.1523/JNEUROSCI.1537-13.2013

MacDonald, C. J., Lepage, K. Q., Eden, U. T., & Eichenbaum, H. (2011). Hippocampal “time cells” bridge the gap in memory for discontiguous events. *Neuron*, *71*(4), 737–749. https://doi.org/10.1016/j.neuron.2011.07.012

Magliano, J. P., & Zacks, J. M. (2011). The impact of continuity editing in narrative film on event segmentation. *Cognitive Science*, *35*(8), 1489–1517. https://doi.org/10.1111/j.1551-6709.2011.01202.x

Maguire, E. A., & Hassabis, D. (2011). Role of the hippocampus in imagination and future thinking. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(11), 2011. https://doi.org/10.1073/pnas.1018876108

Mankin, E. A., Sparks, F. T., Slayyeh, B., Sutherland, R. J., Leutgeb, S., & Leutgeb, J. K. (2012). Neuronal code for extended time in the hippocampus. https://doi.org/10.1073/pnas.1214107109/-/DCSupplemental.www.pnas.org/cgi/doi/10.1073/pnas.1214107109

Manns, J. R., Howard, M. W., & Eichenbaum, H. (2008). the Order of Events. *Memory*, *56*(3), 530–540.

Mau, W., Sullivan, D. W., Kinsky, N. R., Hasselmo, M. E., Howard, M. W., Mau, W., … Howard, M. W. (2018). The Same Hippocampal CA1 Population Simultaneously Codes Temporal Information over timescales Article The Same Hippocampal CA1 Population Simultaneously Codes Temporal. *Current Biology*, *28*(10), 1499–1508.e4. https://doi.org/10.1016/j.cub.2018.03.051

Mayes, A. R., Isaac, C. L., Holdstock, J. S., Hunkin, N. M., Montaldi, D., Downes, J. J., … Roberts, J. N. (2001). Memory for single items, word pairs, and temporal order of different kinds in a patient with selective hippocampal lesions. *Cognitive Neuropsychology*, *18*(2), 97–123. https://doi.org/10.1080/02643290125897

McDermott, K. B., Szpunar, K. K., & Christ, S. E. (2009). Laboratory-based and autobiographical retrieval tasks differ substantially in their neural substrates. *Neuropsychologia*, *47*(11), 2290–2298. https://doi.org/10.1016/j.neuropsychologia.2008.12.025

McNaughton, B. L., Battaglia, F. P., Jensen, O., Moser, E. I., & Moser, M.-B. (2006). Path integration and the neural basis of the “cognitive map”. *Nature Reviews. Neuroscience*, *7*(8), 663–678. https://doi.org/10.1038/nrn1932

Mesulam, M. M., Mufson, E. J., Wainer, B. H., & Levey, A. I. (1983). Central cholinergic pathways in the rat: An overview based on an alternative nomenclature (Ch1-Ch6). *Neuroscience*, *10*(4), 1185–1201. https://doi.org/10.1016/0306-4522(83)90108-2

Milner, B. (1962). Physiologie de l’Hippocampe: Colloque International, No. 107, Editions du Centre National de la Recherche Scientifique, Paris, 1962. 512 pp. 58NF. *Neuropsychologia*, *3*(3), 273–277. https://doi.org/10.1016/0028-3932(65)90029-1

Montchal, M. E., Reagh, Z. M., & Yassa, M. A. (2019). Precise temporal memories are supported by the lateral entorhinal cortex in humans, *22*(2), 284–288. https://doi.org/110.1016/j.bbi.2017.04.008

Mundy, M. E., Downing, P. E., Dwyer, D. M., Honey, R. C., & Graham, K. S. (2013). A Critical Role for the Hippocampus and Perirhinal Cortex in Perceptual Learning of Scenes and Faces: Complementary Findings from Amnesia and fMRI. *Journal of Neuroscience*, *33*(25), 10490–10502. https://doi.org/10.1523/jneurosci.2958-12.2013

Murray, E. A., & Yassa, M. A. (2017). Pattern separation, 1–31.

Nadel, L., Hoscheidt, S., & Ryan, L. R. (2013). Spatial cognition and the hippocampus: the anterior-posterior axis. *Journal of Cognitive Neuroscience*, *25*(1), 22–28. https://doi.org/10.1162/jocn_a_00313

Naya, Y., & Suzuki, W. A. (2011). Integrating what and when across the primate medial temporal lobe. *Science*, *333*(6043), 773–776. https://doi.org/10.1126/science.1206773

Newtson, D., & Engquist, G. (1976). The perceptual organization of ongoing behavior. *Journal of Experimental Social Psychology*, *12*(5), 436–450. https://doi.org/10.1016/0022-1031(76)90076-7

No Title. (n.d.). Graphpad Prism. Retrieved from www.graphpad.com

Nyberg, L., Forkstam, C., Petersson, K. M., Cabeza, R., & Ingvar, M. (2002). Brain imaging of human memory systems: Between-systems similarities and within-

system differences. *Cognitive Brain Research*, *13*(2), 281–292. https://doi.org/10.1016/S0926-6410(02)00052-6

Palombo, D. J., Keane, M. M., & Verfaellie, M. (2016). Does the hippocampus keep track of time? *Hippocampus*, *26*(3), 372–379. https://doi.org/10.1002/hipo.22528

Pastalkova, E., Itskov, V., Amarasingham, A., and Buzsáki, G. (2008). Internally Generated Cell Assembly Sequences in the Rat Hippocampus. *Science*, *321*(5894), 1322–1327. https://doi.org/10.1126/science.1159775.Internally

Paz, R., Gelbard-Sagiv, H., Mukamel, R., Harel, M., Malach, R., & Fried, I. (2010). A neural substrate in the human hippocampus for linking successive events. *Proceedings of the National Academy of Sciences*, *107*(13), 6046–6051. https://doi.org/10.1073/pnas.0910834107

Pierce, J., Gray, J. R., Simpson, S., MacAskill, M., Höchenberger, R., Sogo, H., … Kastman, E. (2019). PsychoPy2: Experiments in behavior made easy. *Behavior Research Methods*, *51*, 195–203. https://doi.org/10.3758/s13428-018-01193-y

Pirogovsky, E., Holden, H., Jenkins, C., Peavy, G., Salmon, D., Galasko, D., & Gilbert, P. E. (2013). 基因的改变 NIH Public Access. *Exp Aging Res*, *39*(4), 371–381. https://doi.org/10.1038/jid.2014.371

Poldrack, R. A. (2006). Can cognitive processes be inferred from neuroimaging data? *Trends in Cognitive Sciences*, *10*(2), 59–63. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16406760

Ramos, J. M. J. (2002). The perirhinal cortex and long-term spatial memory in rats. *Brain Research*, *947*, 294–298.

Ranganath, C., & Hsieh, L.-T. (2016). The hippocampus: a special place for time. *Annals of the New York Academy of Sciences*, 1–18. https://doi.org/10.1111/nyas.13043

Ranganath, C., & Ritchey, M. (2012). Two cortical systems for memory-guided behaviour. *Nature Reviews. Neuroscience*, *13*(10), 713–726. https://doi.org/10.1038/nrn3338

Rauschecker, J. P. (2013). *Neural Correlates of Auditory Cognition* (Vol. 45). https://doi.org/10.1007/978-1-4614-2350-8

Reagh, Z. M., Noche, J. A., Tustison, N. J., Delisle, D., Murray, E. A., & Yassa, M. A. (2018). Functional Imbalance of Anterolateral Entorhinal Cortex and Hippocampal Dentate/CA3 Underlies Age-Related Object Pattern Separation Deficits. *Neuron*, *97*(5), 1187–1198.e4. https://doi.org/10.1016/j.neuron.2018.01.039

Reagh, Z. M., Watabe, J., Ly, M., Murray, E., & Yassa, M. a. (2014). Dissociated signals in human dentate gyrus and CA3 predict different facets of recognition memory. *The Journal of Neuroscience*, *34*(40), 13301–13313. https://doi.org/10.1523/JNEUROSCI.2779-14.2014

Reagh, Z. M., & Yassa, M. a. (2014). Object and spatial mnemonic interference differentially engage lateral and medial entorhinal cortex in humans. *Proceedings of the National Academy of Sciences of the United States of America*. https://doi.org/10.1073/pnas.1411250111

Rogalski, E., Stebbins, G. T., Barnes, C. A., Murphy, C. M., Stoub, T. R., George, S., … DeToledo-Morrell, L. (2012). Age-related changes in parahippocampal white matter integrity: A diffusion tensor imaging study. *Neuropsychologia*, *50*(8), 1759–1765. https://doi.org/10.1038/jid.2014.371

Rolls, E. T., & Kesner, R. P. (2006). A computational theory of hippocampal function, and empirical tests of the theory. *Progress in Neurobiology*, *79*(1), 1–48. https://doi.org/10.1016/j.pneurobio.2006.04.005

Ryan, L., Lin, C.-Y., Ketcham, K., & Nadel, L. (2010). The role of medial temporal lobe in retrieving spatial and nonspatial relations from episodic and semantic memory. *Hippocampus*, *20*(1), 11–18. https://doi.org/10.1002/hipo.20607

Salz, X. D. M., Tiganj, X. Z., Khasnabish, X. S., Kohley, X. A., Sheehan, X. D., Howard, M. W., & Eichenbaum, X. H. (2016). Time Cells in Hippocampal Area CA3, *36*(28), 7476–7484. https://doi.org/10.1523/JNEUROSCI.0087-16.2016

Save, E., & Sargolini, F. (2017). Disentangling the Role of the MEC and LEC in the Processing of Spatial and Non-Spatial Information: Contribution of Lesion Studies. *Frontiers in Systems Neuroscience*, *11*(October), 1–9. https://doi.org/10.3389/fnsys.2017.00081

Schapiro, A. C., Rogers, T. T., Cordova, N. I., Turk-Browne, N. B., & Botvinick, M. M. (2013). Neural representations of events arise from temporal community structure. *Nature Neuroscience*, *16*(4), 486–492. https://doi.org/10.1038/nn.3331

Schröder, T. N., Haak, K. V., Jimenez, N. I. Z., Beckmann, C. F., & Doeller, C. F. (2015). Functional topography of the human entorhinal cortex. *ELife*, *4*(JUNE), 1–17. https://doi.org/10.7554/eLife.06738

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *20*(11), 11–21. https://doi.org/10.1136/jnnp.20.1.11

Seewald, P. M., De Jesus, S. Y., Graves, L. V., Moreno, C. C., Mattson, S. N., & Gilbert, P. E. (2017). Age-related differences on a new test of temporal order memory for everyday events. *Aging, Neuropsychology, and Cognition*, *00*(00), 1–14. https://doi.org/10.1080/13825585.2017.1298716

Semon, R. (1921). *The Mneme*. London: Allen & Unwin.

Shimamura, A. P., Janowsky, J. S., & Squire, L. R. (1990). Memory for the temporal order of events in patients with frontal lobe lesions and amnesic patients. *Neuropsychologia*, *28*(8), 803–813. https://doi.org/10.1016/0028-3932(90)90004-8

Sols, I., DuBrow, S., Davachi, L., & Fuentemilla, L. (2017). Event boundaries trigger rapid memory reinstatement of the prior events to promote their long-term memory., *27*(22), 3499–3504. https://doi.org/10.1002/cncr.27633.Percutaneous

Speer, N. K., Zacks, J. M., & Reynolds, J. R. (2007). Human brain activity time-locked to narrative even boundaries. *Psychol. Sci.*, *18*(5), 449–455. Retrieved from http://dx.doi.org/10.1111/j.1467-9280.2007.01920.x

Spiers, H. J., Burgess, N., Hartley, T., Vargha-Khadem, F., & O'Keefe, J. (2001). Bilateral hippocampal pathology impairs topographical and episodic memory but not visual pattern matching. *Hippocampus*, *11*(6), 715–725. https://doi.org/10.1002/hipo.1087

St. Jacques, P. L., Olm, C., & Schacter, D. L. (2013). Neural mechanisms of reactivation-induced updating that enhance and distort memory. *Proceedings of the National Academy of Sciences*, *110*(49), 19671–19678. https://doi.org/10.1073/pnas.1319630110

Staresina, B. P. (2006). Differential Encoding Mechanisms for Subsequent Associative Recognition and Free Recall. *Journal of Neuroscience*, *26*(36), 9162–9172. https://doi.org/10.1523/jneurosci.2877-06.2006

Staresina, B. P., Duncan, K. D., & Davachi, L. (2011). Perirhinal and Parahippocampal Cortices Differentially Contribute to Later Recollection of Object- and Scene-Related Event Details. *Journal of Neuroscience*, *31*(24), 8739–8747. https://doi.org/10.1523/jneurosci.4978-10.2011

Stark, S. M., Reagh, Z. M., Yassa, M. A., & Stark, C. E. L. (2018). What's in a context? Cautions, limitations, and potential paths forward. *Neuroscience Letters*, *680*, 77–87. https://doi.org/10.1016/j.neulet.2017.05.022

Stoub, T. R., Barnes, C. A., Shah, R. C., Stebbins, G. T., Ferrari, C., & DeToledo-Morrell, L. (2012). Age-related changes in the medial temporal lobe: the parahippocampal white matter region. *Neurobiol Aging*, *33*(7), 1168–1176. https://doi.org/10.1038/jid.2014.371

Suzuki, W. A. (1996). Neuroanatomy of the monkey entorhinal, perirhinal and parahippocampal cortices: Organization of cortical inputs and interconnections with amygdala and striatum. *Seminars in Neuroscience*, *8*(1), 3–12. https://doi.org/10.1006/smns.1996.0002

Suzuki, W. A., & Amaral, D. G. (1994). Perirhinal and parahippocampal cortices of the macaque monkey: Cortical afferents 4025. *Journal of Comparative Neurology*, *350*, 497–533. https://doi.org/10.1002/cne.903500402

Suzuki, W. a, Zola-Morgan, S., Squire, L. R., & Amaral, D. G. (1993). Lesions of the perirhinal and parahippocampal cortices in the monkey produce long-lasting memory impairment in the visual and tactual modalities. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *13*(6), 2430–2451.

Swallow, K. M., Zacks, J. M., & Abrams, R. A. (2009). Event boundaries in perception affect memory encoding and updating. *Journal of Experimental Psychology: General*, *138*(2), 236–257. https://doi.org/10.1037/a0015631

Team, Rs. (n.d.). RStudio: Integrated Development for R. Boston, MA: RStudio Inc., http://www.rstudio.com.

Teyler, T. J., & Discenna, P. (1986). The Hippocampal Memory Indexing Theory. *Behavioral Neuroscience*, *100*(2), 147–154. https://doi.org/10.1037/0735-7044.100.2.147

Thavabalasingam, S., O'Neil, E. B., Tay, J., Nestor, A., & Lee, A. C. H. (2019). Evidence for the incorporation of temporal duration information in human hippocampal long-term memory sequence representations. *Proceedings of the National Academy of Sciences*, *116*(13), 6407–6414. https://doi.org/10.1073/pnas.1819993116

Tsao, A., Sugar, J., Lu, L., Wang, C., Knierim, J.J., Moser, M., and Moser, E. I. (2018). Time coding in lateral entorhinal cortex.

Tsao, A., Sugar, J., Lu, L., Wang, C., Knierim, J. J., Moser, M. B., & Moser, E. I. (2018). Integrating time from experience in the lateral entorhinal cortex. *Nature*, *561*(7721), 57–62. https://doi.org/10.1038/s41586-018-0459-6

Tubridy, S., & Davachi, L. (2011a). Medial temporal lobe contributions to episodic sequence encoding. *Cerebral Cortex (New York, N.Y. : 1991)*, *21*(2), 272–280. https://doi.org/10.1093/cercor/bhq092

Tubridy, S., & Davachi, L. (2011b). Medial temporal lobe contributions to episodic sequence encoding. *Cerebral Cortex*, *21*(2), 272–280. https://doi.org/10.1093/cercor/bhq092

Vazdarjanova, A., & Guzowski, J. F. (2004). Differences in Hippocampal Neuronal Population Responses to Modifications of an Environmental Context: Evidence for Distinct, Yet Complementary, Functions of CA3 and CA1 Ensembles. *Journal of Neuroscience*, *24*(29), 6489–6496. https://doi.org/10.1523/jneurosci.0350-04.2004

West, R. L., & Stone, K. R. (2013). Age differences in eyewitness memory for a realistic event., *69*, 338–347. https://doi.org/10.1093/geronb/gbt014.

Witter, M. P., Naber, P. A., Van Haeften, T., Machielsen, W. C. M., Rombouts, S. A. R. B., Barkhof, F., … Lopes Da Silva, F. H. (2000). Cortico-hippocampal communication by way of parallel parahippocampal-subicular pathways. *Hippocampus*, *10*(4), 398–410. https://doi.org/10.1002/1098-1063(2000)10:4<398::AID-HIPO6>3.0.CO;2-K

Zacks, J. M., Speer, N. K., Swallow, K. M., Braver, T. S., & Reynolds, J. R. (2007). Event Perception: A Mind/Brain Perspective. *Psychological Bulletin*, *133*(2), 273–293. https://doi.org/10.1037/0033-2909.133.2.273

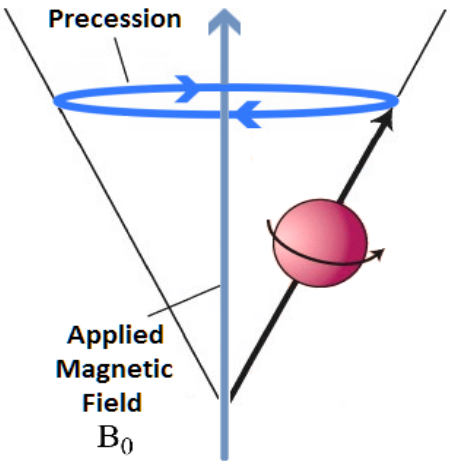
Zemla, R. & Basu, J. (2016). Hippocampal function in rodents, *118*(24), 6072–6078. https://doi.org/10.1002/cncr.27633.Percutaneous

Zola-Morgan, S., & Squire, L. R. (1984). Preserved Temporal Cognitive Learning Lesions : Skills ' in Monkeys With Sparing of Motor Medial. *The Journal of Neuroscience*, *4*(4), 1072–1085.

Appendix: Strengths and Limitations of FMRI

The ability to view the brain noninvasively has led to incredible progress in understanding the neurobiology of learning and memory. It has allowed us to better bridge between human and non-human animal studies. Additionally, it has allowed us to test the role of different brain regions in complex tasks that would not otherwise be possible. In order to interpret MRI studies responsibly, it is critical to understand how the BOLD signal relates to neural activity and the limitations of this powerful technology.

Basic MR Physics



Supplementary Figure 1: A schematic of atomic nuclei precession, courtesy of My-MS.org (2019).

A critical feature of an MRI scanner is that it includes an extremely strong magnet (typically 3 Tesla). This magnet, combined with other components of the MRI scanner, manipulates protons in a way that allows different types of tissues to be distinguished from each other and eventually an image to be produced.

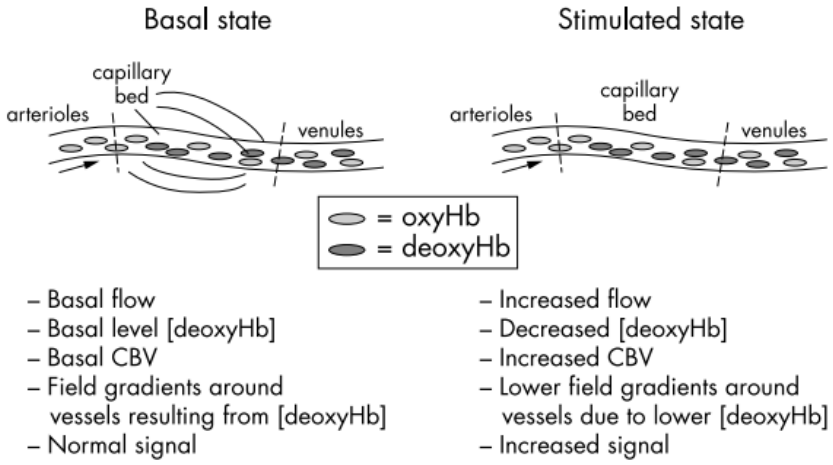
Under normal conditions, protons are aligned in random directions. Inside the magnetic field of the MRI scanner, the protons become aligned with the magnetic field and precess (or spin, like a top. See **Supplementary Figure 1**).

During MRI scanning, special coils emit radiofrequency (RF) pulses that excite the protons and cause them to "tip over". Instead of being aligned with the direction of the magnetic field, they become aligned to the transverse plane. Once the RF pulse is over, they slowly return to precessing around the magnetic field. As they do this, they are not in phase with each other anymore. The time it takes for the protons to go back to their previous orientation, before the RF pulse (relaxation time), is different for different types of tissue. As protons return to their pre-RF pulse orientation, they emit information that can be measured by a receiver coil. After several transformations, this information can be converted to a brain image (Lindquist & Wager, 2014).

Functional MRI

In functional MRI, Two variables allow us to control the contrast, or what is being measured in the tissue: the time between successive RF pulses (repetition time, or TR) and how soon data collection begins after RF pulses are sent (echo time, or TE). Combinations of these variables are associated with different contrasts, named after the time constant associated with their relaxation time. Functional MRI is typically T2* weighted. This is similar to T2 contrast, except that it also capitalizes on

inhomogeneities from oxygenated and deoxygenated blood. When a brain region is activated, blood flow to that region increases, and this can be measured in a series of T2* brain images (see **Supplementary Figure 2**). Changes in blood flow are associated with changes in magnetic properties of the blood which are measured in fMRI (Glover, 2011; Lindquist & Wager, 2014). It is important to note that fMRI does not directly measure neural activity, but blood-oxygen-level dependent (BOLD) fMRI has been shown to correlate with the local field potential (LFP) (Logothetis, 2002).



Supplementary Figure 2: Schematic demonstrating how changes in brain activity translate to changes in blood flow. These, in turn, translate to changes in field gradients and increased signal.

Limitations and Precautions for fMRI studies

Spatial and temporal resolution. MRI researchers want to collect data with the smallest voxels (3-dimensional pixels) possible, in order to clearly view and test hypotheses about small brain regions that may be close to each other. Advances in neuroimaging have led to the point where 1.5-2mm voxels are fairly common in functional data, allowing researchers to examine smaller medial temporal lobe regions. Structural images can

have even higher resolution, although this has limited utility when combined with lower-resolution functional data. Further attempts to increase spatial resolution are often thwarted by poor signal-to-noise resolution.

Temporal resolution is not a strength of fMRI. The hemodynamic response function peaks 5-6 seconds after the onset of a stimulus. As a result, it is difficult to pull apart brain responses to stimuli that always occur close together in time (Glover, 2011; Lindquist & Wager, 2014). Fortunately, experimental design can help with this somewhat (see below).

Artifacts/noise. Artifacts can be seen as a result of certain retainers in participants' mouths or other MR-compatible implants. Other potential issues include heart rate and respiration which can be monitored and regressed out of the data. Participant movement, magnetic field inhomogeneities, and slow drift of the signal over time also cause problems. Fortunately, there are techniques and preprocessing steps to help correct for these problems (Lindquist & Wager, 2014).

Experimental design can help researchers pull apart trials that occur close in time (<5 seconds), which is otherwise difficult due to the slowness of the hemodynamic response. One approach is to jitter trials so that they are different lengths of time apart. This allows sampling of different parts of the hemodynamic response for different trials,

which better allows the researcher to characterize the hemodynamic response for the trial type of interest (Glover, 2011; Lindquist & Wager, 2014). Another approach, which was used in the current work, is to have a consistent inter-trial-interval, but base trial categorization on the participant's performance. In this case, trials were deemed "most precise", "medium precision", or "least precise" based on the participant's answer. Because trials were randomized and behavior is somewhat random, this allowed for a sort of jitter, where trial types were relatively intermixed.

Interpretations. As outlined by Poldrack (2006), caution should be exerted when interpreting fMRI findings. In particular, observing activation of a brain region does not necessarily mean that the function typically associated with that region is involved in the task. For example, finding the prefrontal cortex is preferentially activated for one condition does not mean executive functioning is necessarily involved or more important in that condition. If this hypothesis is important and of interest, it should be tested more directly. For this example, a researcher could see if performance on the task correlates with tests of executive functioning, or design two variants of the task that require more or less cognitive control.