

**HORROR-EVOKED AROUSAL AND AMYGDALA BIAS OF THE  
MEDIAL TEMPORAL LOBE**

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DOCTOR OF PHILOSOPHY

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## ABSTRACT

The ability to learn and predict threats in our environment has a direct impact on what and how we encode our experiences into future recollections. Experience of our daily lives has implications for how we eventually gain long-term memory, adaptive strategies to assess and foresee threats are crucial for survival. Yet, how humans encode threat-related experiences is difficult to study in terms of episodic memory (Clewett & Murty, 2019; Murty et al., 2012). From background literature, a model that focuses on brain-related modulation at encoding which then is found to impact the formation and recollection of episodic experience, our recent work has begun to characterize how threat-related arousal either enhances or disrupts temporal order memory (Cliver et al., 2024; Gregory & Murty, n.d.). In both behavioral (Study 1 and Study 2) and neuroimaging (Study 2) analyses to investigate the relationship between threat-related neural circuitry during encoding of short movie clips to test temporal order memory and temporal distance memory. We measured neural circuitry in the medial temporal lobe (MTL), including the amygdala sub-nuclei areas of the basolateral and the central-medial amygdala, the anterior and posterior hippocampus, and the perirhinal cortex. We present neural univariate signals of these regions of interest (ROIs), and functional connectivity between ROIs (basolateral and central-medial amygdala, anterior and posterior hippocampus, perirhinal cortex) to see successful temporal order memory performance and compression or expansion of temporal distance memory. This work highlights the importance of understanding neural processes of threat-related arousal encoding.

I dedicate this dissertation to my parents, Hayden and Julie, who have supported my joy, comforted my fears, and encouraged my dreams.

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# CHAPTER 1

## INTRODUCTION

The developed theories, methodology, and findings presented within this dissertation can be found within the sentiment of an exchange between characters in a Tennessee Williams play:

*[Character One]: Has it ever struck you, [Character Two], that life is all memory except for the one present moment that goes by you so quick you hardly catch it going? It's really all memory, [Character Two], except for each passing moment. (Williams, 1964)*

Memory, as noted by E. Phelps (2006), is often a nomenclature for our ability to remember past events and facts – however, the exchange in this scene raises a line of thinking about memory that if true, at the time of recollection, our memory is dependent on the events of passing moments and how we can understand today's events as they pass, may help us better understand memory in full. Following this logic, we worked hard to design a methodological approach to measure which experiences of the day impact subsequent memory and how events within these experiences influence future remembrance. If events of today are truly impactful to the formation of memory, one way to approach this topic is within the realm of threat-related arousal memory.

Imagine walking around a foreign city on a long vacation and encountering an unexpected danger that is entirely external, such as seeing a conflict between police and protestors on the way to a famous landmark. Although the tourist has no physical involvement with either police or protestors and is not aware of the exact nature of the conflict, still, that person suddenly experiences an emotional response to the perceived threat in the form of psychophysiological arousal (e.g., the heart starts racing, palms begin sweating with feelings of stress and/or anxiety). During the initial interaction,

threat-related arousal may help or hinder how we encode this real-world experience as our brain transforms it into stored neural information of long-term memory. For example, we may end up having a better overall memory about the moments we approach and encounter the conflict, accentuating details of the clash between police and protesters, which may functionally lead to disruption of memory for the moments after moving away from the encounter and/or details of the landmark eventually visited, which was the original intent of the journey that day. While many great minds have provided brilliant answers about how encoded memories are influenced by heightened psychophysiological arousal to an external threat, there remain twice as many unanswered questions along with the progress. One is the fact that arousal has been shown to both improve and impair memory (Murty & Adcock, 2017). Another is that threat-related memory areas of the brain have shown differential improvements or impairments (Clewett & Murty, 2019). Here, we aim to add to our understanding of the neural mechanisms of threat-related arousal on memory by expanding into the domain of temporal memory from the perspective of cognitive neuroscience and psychology.

The exploration into arousal and memory as they contribute to different mood and anxiety disorders has emphasized emotional regulation difficulties (Shepherd & Wild, 2014). These difficulties may be related to the intensity of the encoding experience, which then results in symptoms of post-traumatic stress disorder (PTSD). For example, individuals with PTSD who have experienced an external traumatic event may emerge with symptoms of hyperarousal (Gootzeit & Markon, 2011). These individuals also show memory deficits related to the event that triggered PTSD (Brewin, 2014). However it is well documented that trauma experience does not uniformly lead towards disorder, and it

has been suggested that differences in arousal responses at the time of encoding may be a predictor of these memory-centered disorders (Rubin et al., 2016). Yet, basic aspects of non-trauma threat experience are still either unclear or understudied, which was an important factor motivating the research presented within this dissertation.

Beyond disorders, the human capacity to learn from threatening situations is crucial for survival, because we use representations of past threats to help avoid harm in the future. The influence of threats on memory is complex, with research showing both improvements and/or impairments in memory performance. While a large body of work shows that threats can enhance memory for the source of the threat and lead to impairments of surrounding contextual details, research has yet to determine threat-related impacts on memory using the element of time. In the context of memory, time refers to a person's ability to recollect an experience in both terms of what happened during an experience to provide temporal context and how it happened with items and events being bound to a context, which combines to help form a cohesive memory of the event (Manning et al., 2014; Tulving, 2002).

Temporal memory is dictated by representations of the temporal order of occurrences as we encounter them, allowing us to resolve the way events, objects, and their relation to situational context unfold over time during an experience. This feature of temporal memory, in addition to the ability to estimate elapsed time, shapes our perception of the temporal distance between events and items within an experience. In this way, temporal memory helps in identifying predictors of upcoming threats or the causal relationships between actions and harm. In sum, temporal memory during a threat necessitates the ability to know what events came first and how the timescales of these

events were experienced. Here, we will characterize threat-related arousal to examine the bias of temporal order memory using ecologically valid practices in cognitive neuroscience.

## **Roadmap to this Dissertation**

The goal of this dissertation is to explore the neural underpinnings of threat-related arousal during encoding on subsequent representations of temporal memory. In Chapter 1, we first provide a theoretical background that is necessary to understand the primary scope of this research. This includes an overview of important concepts, findings, and open questions about the relationship between threat-related arousal, encoding, and recollected memory. This section includes a discussion of both behavioral and neural aspects that will provide a foundation for our theoretical framework. In Chapter 2, we present the approach used in this study and detail our methods and analyses. In Chapter 3, results of the influence of threat-related arousal and neural findings on temporal order memory are presented and discussed. In Chapter 4, results of the influence of threat-related arousal and neural findings on temporal distance memory are presented and discussed. Finally, in Chapter 5 we end with a discussion of these results interpreted in the context of the broader theoretical framework introduced in Chapter 1, limitations of our studies, and future directions.

## **Theoretical Background**

### ***Threat-related Memory***

Threat-related memory research has shown that emotionally salient cues improve memory which is due in part to enhanced perception and attention during encoding. Emotional experiences are often characterized along two dimensions, arousal, and

valence, which are both known to be important in self-report of episodic memory (LaBar & Cabeza, 2006). Studies of arousal characterize memory when one feels calm with low arousal, versus excited/stimulated with high arousal, during encoding. Studies of valence characterize memory depending on how positive or negative the emotions are relating to a stimulus. Both arousal and valence are important features of threat memory, although most studies either emphasize emotional arousal (Anderson et al., 2006; Bradley et al., 1992; Cahill & McGaugh, 1998) or emotional valence (Maratos et al., 2001; Sergerie et al., 2008).

Threat-related memory research has found that arousal can amplify sensory and physiological reactions with heightened awareness, which increases reliance on an adaptive learning process to enhance long-term memory for events (Storbeck & Clore, 2011; Tanriverdi et al., 2022; Wang & Yang, 2017). Threat-related memory research has shown that negative valence, which is often associated with threats, impacts memory for real-life environments (Chiew & Adcock, 2019), increases vividness (Kensinger & Corkin, 2004), prioritizes negative events in memory (Rosenbaum et al., 2022), and may alter long-term memory of threat experiences via defensive behavior towards threats in spatial proximity (Åhs et al., 2015). Often arousal and valence are shown to have combined impacts on threat-related memory, such that an effect of arousal within the emotional memory network may depend on item valence (Steinmetz & Kensinger, 2013), with contrasting enhancements for positive stimuli which may target associative memory, and negative stimuli which may target item memory (Clewett & McClay, 2024; Clewett & Murty, 2019; Kensinger, 2004, 2009; Madan et al., 2019; Pierce & Kensinger, 2011). While both valence and arousal may be equally important, arousal may create a biased

effect towards item/relational memory, but previous studies have only included neutral and aversive (threat-related) stimuli, which ultimately was not designed to dissociate valence along the spectrum of positive to negative.

In summation, when considering arousal and valence, the background research has led us to theoretically determine our focus on arousal. The major reason as described in Chapter 2, is that our studies use aversive contextual manipulation with temporal order measures, and specifically are concerned with how arousal impacts our threat-related encoding studies. Valence in memory studies may be better understood using positive stimuli along with negative stimuli (Kauschke et al., 2019), since describing ‘negative’ valence may rely on ‘positive’ valence stimuli for a full scope of behavioral impact. Further, findings in the literature on valence beyond memory describe both a ‘positivity effect’ (Leppänen & Hietanen, 2004; Nummenmaa & Calvo, 2015), and a ‘negativity effect’ (Dijksterhuis & Aarts, 2003; Nasrallah et al., 2009). Second, the questions we ask within this dissertation have been used to describe both animals and humans (Eilam et al., 2011; Kaźmierowska et al., 2023; Pape & Paré, 2010). Threat-related detection arousal was paramount in our stimuli selection and designing our encoding and memory task measures. As such, our research approach focuses on arousal as the primary variable across studies presented in Chapters 2-4.

### ***Threat-related Neural Circuitry***

Psychological processes in response to danger are dependent on different neural circuits with distinct computations influencing behavior. Understanding these computations at the neural level, and their controlling actions may be described as the underlying threat-related neural circuitry. Here, we focus on the amygdala in the scope of

threats, arousal, and memory. Although there may be a wider role of sensory and cognitive facets that relate to threats in additional cortical and sub-cortical areas, brainstem, and cerebellar areas, this dissertation was developed to better understand the specifics of the memory areas described below. Looking into modulatory factors and functional activity in brain regions that are not within the scope of this dissertation is an important direction for future consideration and will be discussed briefly in Chapter 5.

A primary goal of the studies described in Chapters 2-4 is to characterize the encoding of arousal-driven threat-detection behavior during functional imaging in order to better understand threat-related memory within the medial temporal lobe (MTL). The MTL is largely known to support memory functions, but a meta-analysis has further identified MTL structures involved in emotional memory encoding, including the amygdala, hippocampus, and perirhinal cortex (Murty et al., 2010), which have yet to be fully described in the context of threat-related arousal influencing temporal memory. But first, we will review the amygdala with a focus on threat-related research, then introduce an argument that the amygdala should not be viewed as a unified structure, and finally describe the direct and indirect relationship of the amygdala with psychophysiological arousal.

The amygdala has long been a focus of emotional behavior (Klüver & Bucy, 1997) and emotional memory (Kensinger & Corkin, 2004). Animal, non-human primate, and lesion work has further characterized the amygdala as a collection of subregions, including basolateral and central-medial amygdala, each with different functional properties. The amygdala is a highly concentrated area in the brain responsible for threat detection during simple danger learning, which has related consequences on memory,

along with an assortment of other behaviors. The current dissertation focus is on emotional memory, with a study designed to limit fear and aggression and examine threat detection during contextual encoding manipulation. In this way, one of the basic known features of the amygdala may be better understood in the context of adaptive memory. In brief, adaptive memory is an evolutionarily based concept within the memory literature, pointing out that learning and memory require consideration within a larger framework of specific important elements (Murty et al., 2016; Ranganath & Ritchey, 2012; Shohamy & Adcock, 2010). A major concern of adaptive memory research is then to understand how functional processes are influenced by environmental elements leading to goal-directed future behaviors, which are preserved by time and the overall ability to recollect. Within supporting literature on memory formation, research reveals that how the amygdala bolsters or impairs memory is not fully understood (Bennion et al., 2013; Cahill & McGaugh, 1998; LaBar & Cabeza, 2006; Murty et al., 2011; Murty & Adcock, 2017; Tyng et al., 2017; Yonelinas & Ritchey, 2015).

Threat processing models of Pavlovian learning are related to clear behavior outcomes (Martínez-Rivera et al., 2019). Animal models have shown that the basolateral is known for active avoidance of threat, whereas the central-medial amygdala is known for freezing response to threat (Goosens & Maren, 2001; Moscarello & Maren, 2018). As such, engagement of these subregions produces different behavioral profiles in animals and may correspond with different encoding strategies in humans, culminating in potential consequences on human memory.

Threat-related arousal within the brain regions of MTL is dramatically impacted due to hypothalamic-pituitary-adrenocortical (HPA) release of bodily hormones from

endocrine sources, which increase circulating levels of adrenaline and noradrenaline, thus resulting in heightened heart rate, peripheral vasoconstriction, and energy mobilization (Buijs & Van Eden, 2000). A major outcome of HPA activity is also seen neurally as a response in the locus coeruleus noradrenergic (LC-NE) neuromodulatory system. The LC-NE is a brain-wide projecting monoamine system, with a role in arousal, stress, and attention, including novelty-driven episodic memory (Jordan, 2024). Importantly, the LC-NE system has been shown to innervate the amygdala (Plummer et al., 2015; Robertson et al., 2016). But this implies a reciprocal nature between physiological arousal and threat-related encoding as the amygdala also plays a role in keeping the endocrine system in balance due to the emotional state (Hu et al., 2022).

Last, there are many documented findings purporting that the amygdala enhances subsequent memory of items following emotional arousal response (Hamann, 2001; Mather, 2007; Phelps, 2006; Phelps & LeDoux, 2005), yet this system has not been fully understood as it relates to the engagement of memory regions (e.g., the hippocampus and perirhinal cortex, described in more detail below). During a threat-related memory task, the MTL has been shown to enhance item memory by biasing from sub-cortical MTL to cortical MTL (Murty et al., 2012). If indeed arousal-driven memory is directed by amygdala sub-nuclei regions which change the relative engagement of sub-cortical areas like the hippocampus and cortical areas like the perirhinal cortex (Murty & Adcock, 2017; Yonelinas & Ritchey, 2015), threat-related factors during encoding may be shown to bias this relationship in ensuing episodic memory in humans.

## ***Episodic Memory***

The impact of threat-related arousal on memory is presented in this dissertation as related to the neurobehavioral mechanisms underlying episodic memory. Episodic memory provides humans with the ability to recollect the experience and events (Allen & Fortin, 2013; Tulving, 2005). Personal experience then dictates episodic memory, which includes recollection of spatial and contextual environmental information, psychophysiological experiences, and, most relevant to this dissertation, the evaluation of temporal experience. As such, this dissertation is focused on encoding features that influence subsequent retrieval. Our studies are designed to impact threat-related arousal using temporal memory measures that depend on encoding experience. As such, in terms of episodic memory, we feel our studies offer insight into behavioral and neural aspects of encoding and follow from theoretical viewpoints.

## ***Episodic Memory Neural Circuitry***

Early influential work in lesion-related findings identified areas of the MTL that may facilitate episodic memory, including the hippocampus and perirhinal cortex (Scoville & Milner, 1957). The hippocampus has differential functionality along its long axis. Anatomical distinctions of the anterior portions and posterior portions of the hippocampus have different roles in network connectivity and grid cell organization, in addition, the hippocampal sub-units perform pattern completion directed in the anterior, while pattern separation is directed in the posterior (Poppenk et al., 2013). Specific to this dissertation, it follows that looking at hippocampal sub-units the anterior hippocampus may support more global representations for experiential events while the posterior hippocampus facilitates more detailed, granular representations, such as item-related

memory of events (Audrain & McAndrews, 2022; Brunec et al., 2018; Sekeres et al., 2018). Finally, during episodic recall, it has been theorized that the anterior hippocampus helps the search and access experiences while the posterior hippocampus expands the episodic details (Devignes et al., 2024), which may vary depending on cortical and sub-cortical inputs (Yavas et al., 2019).

The perirhinal cortex belongs to the cortical-MTL parahippocampal regions that provide polysensory input to the hippocampus. The neural pathway from the perirhinal cortex to the entorhinal cortex is considered one of the main paths into the entorhinal–hippocampal network, which has a crucial role in memory processes. The perirhinal cortex specifically supports higher-level item memory (Davachi, 2006; Davachi et al., 2003; Dougal et al., 2007; Kensinger & Schacter, 2006; Kirwan & Stark, 2004; Ranganath et al., 2004; Uncapher & Rugg, 2005) and sensory modalities may converge in the perirhinal cortex before hippocampus and other cortical-MTL areas (E. A. Murray & Wise, 2012). The perirhinal cortex also interconnects with the amygdala, which has been shown to form an important relationship for motivational and emotional behaviors (Kajiwara et al., 2003); the amygdala was found to modulate hippocampal activity during encoding for source memory and perirhinal cortex activity for items (Ritchey et al., 2019).

### ***Linking Episodic and Threat-related Neural Circuitry***

The neural circuitry of episodic memory which informs this dissertation relies on the fact that the hippocampus and perirhinal cortex have different adaptive responses to novel information (Murty et al., 2013). Adding to this avenue of thought, as mentioned previously, threats have been shown to bias the amygdala to cortical-MTL targets (Murty

et al., 2012), which led us to consider how adaptive memory may be directed by hippocampal and cortical MTL engagement depending on neuromodulatory systems, including LC-NE release via amygdala (Murty & Adcock, 2017). Before moving to better describe temporal memory, next is a quick examination of the connection between the key brain areas we have identified above.

### ***Direct Connections of the MTL***

The neural circuitry of threat-related arousal has been shown between the amygdala, hippocampus, and cortical MTL (Giustino et al., 2020; LeDoux & Daw, 2018; Malivoire et al., 2018; Pitkänen et al., 2000; Figure 1). There is a large amount of non-human primate and other animal research showing that the lateral amygdala, a sub-unit of the basolateral amygdala, which projects to other areas of the brain, has an efferent and afferent reciprocal nature from the hippocampus and other areas (Canteras & Swanson, 1992; Cassell et al., 1999; Krettek & Price, 1977; Savander et al., 1997; Shi & Cassell, 1999). There exists substantial anatomical evidence that the strong reciprocal connections of the amygdala modify the function of the perirhinal cortex and hippocampus via the basolateral amygdala, but there does not exist the same connections via the central-medial amygdala (Maren, 1999; B. D. Murray & Kensinger, 2013). However, the central-medial amygdala receives input from MTL areas and is involved in arousal detection (LaBar & Cabeza, 2006; Pape & Paré, 2010). As such, the amygdala is perhaps better understood in functional roles of modulating emotion which may then bias further MTL areas during encoding. To determine if this is the case, we will look at both basolateral and central-medial amygdala as seed regions to the anterior hippocampus, posterior hippocampus, and perirhinal cortex targets within our models of functional connectivity

to explore what each of these MTL regions contributes to understanding encoding representations in the brain.

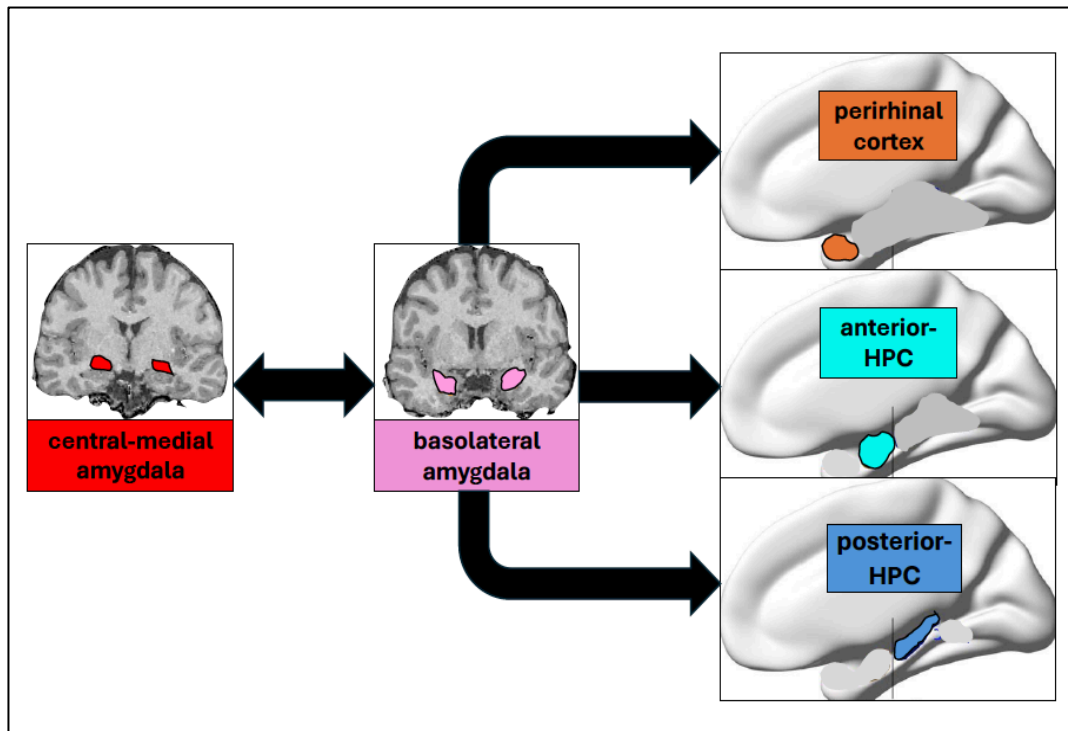


Figure 1: Direct Connections of Threat-related Neural Circuitry of the MTL. Black arrows indicate connections important to threat-related arousal circuitry.

This line of research was investigated previously in our lab, using high-resolution resting-state functional MRI data without threat or any study-specific task (Gregory et al., 2020). We found participants showed biased connectivity between MTL regions, which included amygdala seed regions. We found that the basolateral amygdala showed greater functional coupling with the hippocampus head (which is equivocal to the anterior hippocampus) and perirhinal cortex; however, it is notable that there was also significant connectivity between the central-medial amygdala and the perirhinal cortex. A limitation of this study was that these circuits were characterized during rest, and these interactions may not become more prominent until arousal is present. These findings that the neural

system was not equally engaged by neuromodulatory regions at rest have helped lay the foundation for the direction of the current study.

### ***Temporal Memory***

Since events are stored sequentially, individuals will often recall events in the order in which they were encoded. Temporal memory is then a matter of binding items to temporal context over time as an encoded episode (Howard & Kahana, 2002). Memory contiguity predicts that items that were encoded more closely in time will be recalled together (Howard et al., 2008). Temporal order studies in non-threatening situations have not determined if these processes enhance the salience of individual items in a temporal context (Talmi et al., 2019) or make use of relative memory search to resolve temporal order (DuBrow & Davachi, 2014).

Prior work from our laboratory made use of a staged event as a quasi-naturalistic experimental setting. This staged event was an in-person haunted house with different themed areas that participants walked through sequentially with set-piece events as a feature of the layout (within a large former prison that had been reworked as a historical monument with a portion that is set aside for an annual haunted house set), found that threat-related arousal during encoding was associated with enhanced memory for the temporal order of events. However, characterizing temporal memory in this context was limited by our inability to tightly control the temporal unfolding of threatening events and we were not able to control the nature of intervening events and or the temporal duration of two threat events. Our behavioral findings show that item-time binding is enhanced under threats, specifically during pseudo-naturalistic staged events (Cliver et al., 2024).

Yet open questions remain as to how the MTL responds in the engagement of amygdala sub-nuclei, hippocampus, and cortical-MTL during threat-related arousal.

In full, these findings helped in developing a model to reveal how threat-related arousal biases information processing away from the hippocampus to other learning structures, predominantly due to arousal-mediated engagement of the norepinephrine system (Clewett & Murty, 2019; Murty & Adcock, 2017; Figure 2). This theorized model is proposed to better describe how the neural circuitry has a relationship that is impacted by the encoding environment, in a brain-based arousal model.

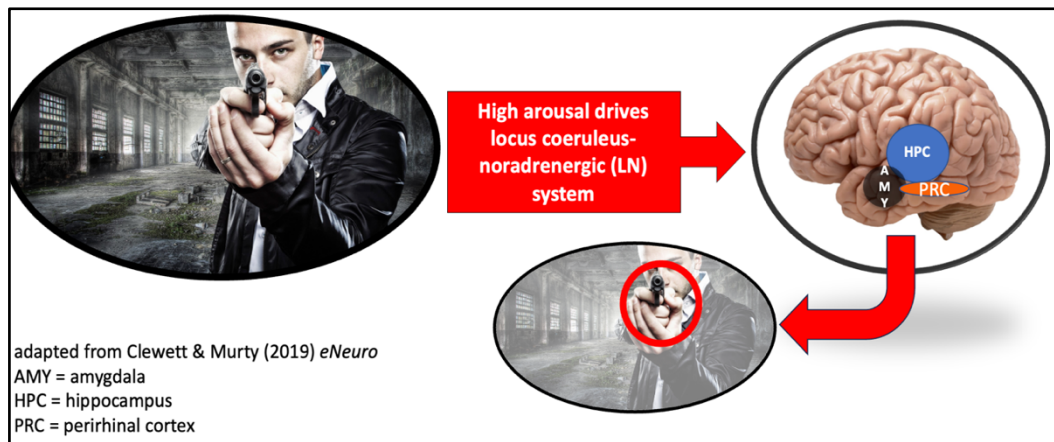


Figure 2: Brain-based Model of Arousal. The model we are testing in this dissertation have been developed following psychophysiological theories presented within Clewett and Murty (2019) *Echoes of Emotions Past: How Neuromodulators Determine What We Recollect*. *eNeuro*, 6 (2). doi.org/10.1523/ENEURO.0108-18.2019.

## Concluding Remarks

The objective of this dissertation is to bring distinct literature together to explore how threat-related arousal influences different aspects of memory. The studies presented in Chapters 2-4 represent ongoing efforts investigating the relationship between threats, arousal, and memory. We navigate the environments of our lives without guarantee of

safety, and many experience traumas without warning or preparation. Further, threat-related arousal is crucial in supporting memory as we encounter new and novel situations which we need to use in episodic memory representations. Yet, it is unclear if our memories are improved or impaired due to arousal.

To resolve the discrepancy of the role of threat-related arousal on memory, we propose a model of encoding in which the sub-nuclei of the amygdala may have divergent functional connectivity to the hippocampus and cortical-MTL which helps us to portray the order of behavior of events as they happen which may be supported by the increased organization of aversive items being enhanced in memory due to heightened arousal (Mao et al., 2017; Tanriverdi et al., 2022). Characterizing the brain-related encoding changes observed while watching a movie clip will better clear the clouded landscape that has surrounded the impacts of threat on memory. This finally leads us to our use of temporal order memory as a basic cognitive function that offers many complicated paths of manipulation; one of which is to better understand how the temporal order of events and time duration are impacted by threat-related arousal encoding.

Temporal memory is crucial for survival and relies on both what happened (specific events) and how it happened (relational) during an encoded event. Threat-driven arousal modulation of the MTL may bias temporal order memory during encoding, as the hippocampus makes use of incoming information from the perirhinal cortex and other areas to combine information into a coherent event of spatiotemporal aspects that layers experience in space and time. If memory biases represent a tradeoff between items being dissociated from their context and item-context cohesion, neuromodulation via amygdala sub-nuclei during arousal-driven events in threat-related memory may help explain

differential findings. Yet, temporal memory research has focused on testing memoranda for static images in lab settings for threat memory which may not fully describe the natural formation of memory (Bouvarel et al., 2022; Kim et al., 2013; Madan et al., 2012; Okada et al., 2011; Steinmetz & Kensinger, 2013).

Utilizing movie clips in temporal studies may offer a balance between the tight control of a laboratory-based study with the natural unfolding of time that is prioritized when using a staged-event or autobiographical memory study. Recently, research using a horror movie found that memory for temporal order was greater for high versus low emotional events (Dev et al., 2022). In this study, participants' memory was characterized by a single clip that was either aversive or neutral, which limits the ability to determine temporal order concerning changing context during an experience. As the researchers were looking at one movie, without alternating conditional effects, it is hard to know if the changing aspects of the affective state are due to stimuli or track the shifting of arousal in a single conditional encoding experience. However, their results do help to bolster the findings presented within this dissertation.

Horror movies have been used in various psychology and neuroscience projects, although often without considering condition (Hudson et al., 2020), but often considering larger topics such as overall fear and anxiety associated with horror movies within the scope of studying this film genre. For our purposes, we selected our stimuli from horror movies for specific reasons, such as matching a neutral clip to an aversive clip within a movie to match the visual characteristics of stimuli across conditions. Further, selecting horror movies for specific types of aversive response (suspense/external threat), and not supernatural/monsters or gory/bloody scenes, was directly implemented to find specific

stimuli for our theoretical concepts of threat-related arousal to fit within our methodological design.

The current studies presented in Chapters 2-4 investigated how varying contextual levels of short movie clips depicting threatening and neutral events extracted from horror movies (one aversive and one neutral clip from each movie) on arousal, and subsequently tested the temporal memory for those events. Specifically, we assessed the memory for the temporal order of events (i.e., recency discrimination) and a retroactive estimation of elapsed time (i.e., distance estimation). Critically, by leveraging self-reports of arousal following the encoding of each movie clip, we were able to dissect how the variability of changing context during encoding influences our measures of temporal memory.

Recency discrimination and distance estimation both rely on relational and item-based memory, but it is reasonable to say that recency discrimination relies more on relational memory or gist/aggregate memory representations, while distance estimation relies more on item-based or fine-grained memory representations. Because recency discrimination of still images does not necessarily have major landmarks or items that have been designated as important, it is more likely the memory of the entire clip will be used to determine an objective answer, correct or incorrect. Further, distance estimation has no still image on screen during the memory task but asks for a determination of how close or far these images are within a movie clip, which allows participants to search their memory for features that define the movie clip, and those that are closer to the previous still images will better help to determine their location within the entire scene.

For this basic, yet complicated system, we have carefully considered how humans may encode a threat-related event at varying levels of arousal. During such an event,

arousal experience can unfold over time in both low and high valleys, which may act as benchmarks of salient events to scaffold the entire episode and its narrative flow. This time element would otherwise be unsupported and could be expanded or compressed due to the environment, emotions, and the subjective perception of time. Here, we predict that these scaffolds will be supported by cortical-MTL-based fine-grained memory, which would highlight salient individual features of an event; and these specific details would help scaffold and support the narrative flow of that event, which is stored in the anterior hippocampus as a more general relative memory trace. Now applying this framework to threats, we think that high levels of arousal will engage the central-medial amygdala, thus allowing the perirhinal cortex to make more items/scaffolds, which in turn will support greater narrative flow which will also be constricted by the central-medial amygdala and anterior hippocampal interactions, while basolateral amygdala will be engaged at lower arousal, impacting the hippocampus to better retain global information.

The overall threat-related arousal memory encoding of arousal would then predict that central-medial amygdala nuclei will bias towards MTL during higher arousal and the basolateral amygdala will bias towards MTL during lower arousal. Largely, this has been formed following animal research showing how high arousal impacts freezing behavior, while lower arousal impacts more fighting and fleeing behavior, which as described above is reliantly dependent on these sub-nuclei areas of the amygdala. This form of neuromodulatory engagement (driven by the locus coeruleus-noradrenergic system) would not fully describe the relationship of threat-related arousal neural circuitry but would help to inform models that may better describe memory improvements at threat-level vs. trauma-level of arousal.

## CHAPTER 2

### INTRODUCTION TO THE CURRENT STUDIES

Our goal for the described methodology in Chapter 2 is to understand how threat-related arousal may impact temporal memory. Static images have been widely used in past research, but here we offer a naturalistic approach to help resolve some of the limitations of prior temporal memory research. We were interested in developing our study directed towards defining mechanisms of two primary neural signals using univariate and functional connectivity analyses to better understand the mechanisms related to threat-related arousal.

Here, we will describe two separate studies that each assay two forms of temporal memory (recency discrimination and distance estimation). In brief, Study 1 is an online behavioral study with an immediate memory test and Study 2 is an in-person, fMRI study with a delay memory test.

#### **Methods Study 1**

##### ***Participants***

Study 1 was conducted following ethical guidelines set by Temple University's Institutional Review Board. Informed consent was obtained from all participants, and they were assured of their confidentiality and right to withdraw at any point during the study. All participants were compensated \$15 per hour of participation (average time = 55 minutes). A total of 184 participants were recruited online via Prolific (<https://www.prolific.com/>). Inclusion criteria included native English speakers, an age range between 18 to 45, the ability to use and access a computer on Prolific, and having a US account on Prolific as all movies were US productions. Exclusion criteria included

performing at chance level or below on the recency discrimination task ( $n = 8$ ) and/or failing the attention checks during encoding ( $n = 8$ ). Our final sample consisted of 168 participants (age range = 18-43; 84 M / 79 F / 1 NB / 4 unknown). Notably, a power analysis from a pilot study ( $n = 33$ ) indicated we would need at least 150 participants to achieve sufficient statistical power (80%) for an expected level of effect size (95%) at a 0.05 significance level.

### ***Stimuli Selection***

Finding a method to evoke arousal that could be performed during fMRI was essential to the foundation of Study 1, but using horror movies also allowed us to find both an aversive and neutral clip from the same movie to better control the changing condition between arousal states as exhibited by the subjects.

We selected ten horror movies from a pool of over 100 available films reviewed on Shudder VOD. These movies were selected to evoke varying levels of negative emotion and arousal across participants. Movies were carefully selected to highlight suspenseful and psychological horror over more overt, bloody/body horror to avoid emotions of disgust and terror, as well knowing participants for Study 2 would be in the fMRI scanner and suspense/psychological horror clips would avoid ‘jump scares’ would, in turn, would limit head motion.

For each movie, we selected two 2-minute clips depicting an aversive scene and a neutral scene. The clips were matched on simple aesthetics using this methodology such that setting, filming, characters, and dialogue/music were taken from the same movies to control for potential confounds as possible when using movie stimuli. When selecting videos, we prioritized balancing the basic features described, as well as finding clips that

contained a full scene including a beginning, middle, and end. All movies selected were small budget or independent to ensure low familiarity of the movie to participants. Notably, each participant only viewed the aversive or neutral clip from each movie during the study.

For the memory retrieval tasks (detailed below), we generated 4 pairs of stills for each movie clip that had a temporal interval of 12 seconds ( $\pm$  3 seconds to find usable still images). These stills were selected to be distributed throughout the clip, resulting in 8 stills per clip. The first and last images were not used in either of our memory tasks to lower the impact of primacy/recency predisposition and build on previous research in our lab (Cliver et al., 2024) and broader temporal memory research indicating the heightened impact of first and last items on subsequent memory (Ezzyat & Davachi, 2014).

### ***Experimental Design***

All experimental procedures were implemented using PsychoPy software (Peirce et al., 2019), hosted on Pavlovia, and disseminated to participants on Prolific, a platform dedicated to recruiting participants for online research studies. The study included an Encoding Phase, a Temporal Memory Phase, and a Questionnaire phase resulting in a study duration of ~50 minutes (Figure 2).

During the encoding phase, participants were instructed they watch movie clips and then rate each clip using measures of arousal, valence, coherence, and familiarity. On each trial, participants first viewed a cue for 5 seconds indicating whether the upcoming clip would be an aversive or neutral video clip. Participants then viewed a movie clip for 120 seconds. Then, participants rated evoked levels of arousal, valence, coherence, and familiarity using a continuous visual analog scale ranging with labeled endpoints.

Participants completed 10 trials in which 5 neutral and 5 aversive clips were presented in a pseudo-randomized order. Pseudo-randomization was achieved by generating 8 different stimulus orders in which no two clips were drawn from the same movie. No more than two movie clips drawn from the same condition could appear in a row, and the encoding phase could not start or end with two movie clips drawn from the same condition.

Following the encoding phase, participants completed a temporal memory task, which probed both recency discriminations and temporal duration estimations. On each trial, participants were presented with a pair of still images extracted from each clip. Participants were then asked to select the clip that appeared first (i.e., recency judgment) and indicate their confidence in the response. Following the recency discrimination judgment, participants had to indicate their estimations of how much time elapsed between the two clips (i.e., temporal distance). Participants completed 80 trials of the memory task, which included stills drawn from previously viewed videos (40 trials), as well as the never-before-seen stills drawn from movie clips that were not shown. For example, if a participant viewed the aversive clip from Movie A, they would also have a trial from a neutral clip drawn from Movie A. The location of the correct response for the recency discrimination task as well as the trial order was randomized across trials.

Following the memory phase, participants completed two questionnaires. They first completed a genre questionnaire, where they indicated their enjoyment on a scale from 1 (“do not enjoy at all”) to 5 (“enjoy very much”) of three genres of films: Horror, Action, and Thriller. This questionnaire aimed to capture individual preferences for different types of emotional clips to assess whether enjoying horror movies influenced

our memory results. Participants then completed the self-report, PTSD Checklist for DSM-5 (results not presented in this dissertation).

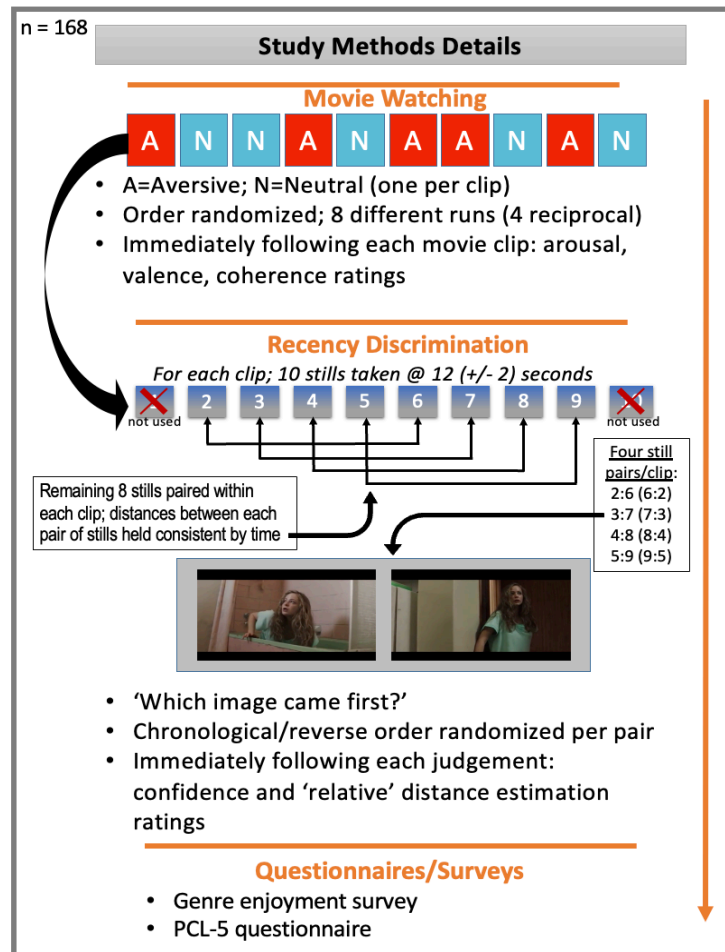


Figure 3: Overview of Methods Study 1. Methods for online, behavioral Study 1 during encoding and memory test.

### ***Statistical Analysis***

All statistical analyses were performed using R Statistical Software (v4.1.2; R Core Team 2021). To assess the role of arousal and valence ratings on memory, linear mixed modeling analyses were conducted using the lmer function from the lme4 packages in R (<http://cran.r-project.org/web/packages/lme4/>). Importantly, we collapsed

across conditions (aversive and neutral) for both behavioral and neural data in all analyses, this was done to better predict how arousal is impacted beyond a primed, behavioral context effect. For significance testing of the multi-level models, we performed a model comparison between a baseline model (which controlled for error terms for participant ID and movie as factor terms) and a model that included the dependent variable of interest using the ANOVA function, which performs a Bayesian Model Comparison. Notably, including stimulus order in our statistical models did not significantly influence the results, so we chose to run our models without this variable. Below, we detail the specific models that we ran using these guidelines, and we report on the best-fit model out of this family of model comparisons for recency discrimination and distance estimation in Chapters 3 and 4, respectively.

All within-encoding scores (arousal, valence) were mean-centered before analyses, such that within-participant scores for these variables for viewed movie clips (i.e., the four scored recency discrimination scores for each movie clip viewed) were averaged around their mean value for each participant for each movie clip. Significance was determined by a p-value  $< 0.05$  and the significance of individual dependent variables was assessed with the lmerTest package. We next describe our model comparison approach to determine the influence of arousal and/or valence on memory.

For the analysis of recency discrimination, we calculated a corrected recency discrimination accuracy score for Study 1. We performed a correction to account for any differences in our stimuli that may have made the recency discrimination task relatively easier or harder for any specific movie clip. We achieved this by having an independent group of ‘naïve’ participants (n=50) perform the recency discrimination task and

calculated ‘chance’ levels of performance on a clip-by-clip basis. We then subtracted an individual subject’s accuracy for a clip against the ‘chance’ score drawn from this independent group. These scores were averaged per movie clip and these final scores were then used in all memory analyses. All recency discrimination scores were then mean-centered.

### ***Approach to Arousal in Behavioral Analyses***

To test for the main effect of arousal on recency discrimination (and for distance estimation) our model comparison included:

- Baseline model: Recency discrimination  $\sim 1 + (1|PID) + (1|movie)$
- Test model: Recency discrimination  $\sim arousal + (1|PID) + (1|movie)$

To test if valence was related to recency discrimination (and for distance estimation) above and beyond arousal, our model comparison included:

- Baseline model: Recency discrimination  $\sim 1 + arousal + (1|PID) + (1|movie)$
- Test model: Recency discrimination  $\sim valence + arousal + (1|PID) + (1|movie)$

These models will be used in behavioral analyses in Study 2, except for the addition of the error term for movie order, but only as a significant variable for distance estimation.

## **Methods Study 2**

### ***Participants***

All participants were recruited from the Temple University community and compensated for their time (\$60 for Day 1 and Day 2), following similar IRB guidelines described above but more comprehensive to include in-person behavioral and fMRI procedures. A total of 47 participants completed the full study out of 48 recruited. We

excluded two participants for data analysis as two Day 1 fMRI data had issues from the scanner that did not allow preprocessing and another due to Day 2 memory test data missing/computer issues. This left us with a total of 44 (M: 18, F: 26, average age = 20 years old) participants for analyses presented here. Inclusion criteria included native English speakers, an age range between 18 to 45, fluent in English and normal or corrected-to-normal vision, and the ability to undergo an MRI test for an hour. A power analysis indicated we would need at least 40 participants to achieve sufficient statistical power (80%) for an expected level of effect size (95%) at a 0.05 significance level.

### ***Study Materials***

We selected six horror movies from the ten final movies used in Study 1. These movies were selected to evoke varying levels of negative emotion and arousal in viewers, also the aversive clip was rated higher in arousal and more negative in valence than the neutral clip for all six movies. Movies were carefully selected to highlight suspenseful and psychological horror over more overt, bloody/body horror because of scanning-related requirements and arousal-related anticipation over disgust. Further, by selecting movies from Study 1 an authentic variety of clips depicted specific thematic elements in different ways (e.g., domestic violence versus suicide), which helped leverage idiosyncratic differences in self-reported ratings of arousal and valence across participants, as well as subsequent memory representations.

### ***Experimental Design***

All experimental procedures included an instruction and encoding phase with a delayed, 24-hour temporal memory/free recall phase and a questionnaire phase resulting in a study duration of two hours over two days (Figure 4).

During the instructions/encoding phase, participants practice watching a movie clip and performing ratings before entering the fMRI. This allowed participants to understand how ratings need to be performed after each clip, with questions of arousal, valence, coherence, and familiarity. A soundcheck was also used to get participants ready for encoding. On each trial, participants first viewed a cue for 5 seconds indicating whether the upcoming clip would be an aversive or neutral video clip. The logic here is that participants are primed for the condition, and do not have to guess the condition as well as make sure that drifting emotional effects are lessened, along with the within-encoding ratings taken after each clip, all help to make sure conditional aspects of our study poignant. Participants then viewed a movie clip for 120 seconds. Then, participants rated evoked levels of arousal, valence, coherence, and familiarity using a continuous visual analog scale with labeled endpoints. Resting fixation cross screens were also interwoven into the study, before and after each movie clip, but will not be included in the current analyses. During the fixation cross, participants were instructed to keep their eyes open, without any other instructions. The time length of 120 seconds was also used to allow for participant emotional, or arousal, overstay. Participants completed 6 separate runs of single movie clip presentation trials with 3 neutral and 3 aversive clips presented in a pseudo-randomized order. Pseudo-randomization was achieved by generating individual stimulus orders in which no two clips were drawn from the same movie. No more than two movie clips drawn from the same condition could appear in a row, and the encoding phase could not start or end with two movie clips drawn from the same condition.

Following the encoding phase, participants returned to the lab after 24 hours to complete a temporal memory task, cued cued-free recall task, and questionnaires. The temporal memory task was designed to probe both recency discriminations and temporal duration estimations. On each trial, participants were presented with a pair of still images extracted from each clip. Participants were asked to select the clip that appeared first (i.e., recency judgment) and indicate their confidence in the response.

Following the recency discrimination judgment, participants indicated their estimations of how much time elapsed between the two clips (i.e., temporal distance). Participants completed 48 trials of the memory task, which included stills drawn from previously viewed videos (24 trials), as well as the never-before-seen stills drawn from movie clips that were not shown (24 trials). For example, if a participant viewed the aversive clip from Movie A, they viewed those image pairs as well as the ones from the neutral clip drawn from Movie A. The location (left or right side of the screen) of the correct response for the recency discrimination task as well as the trial order was randomized across trials. A cued-free recall task was also given, using images not shown during recency discrimination (first and last images, not shown for primacy/recency), but were shown to spark any recollection the participant had of each movie clip. The free recall data will be analyzed in later studies and will not be included in this dissertation analysis.

Following the memory phase, participants completed two questionnaires. They first completed a genre questionnaire, where they indicated their enjoyment on a scale from 1 (“do not enjoy at all”) to 5 (“enjoy very much”) of three genres of films: Horror, Action, and Thriller. This questionnaire was aimed to capture individual preferences for

different types of emotional clips to assess whether enjoying horror movies influenced our memory results. Participants then completed the self-report, PTSD Checklist for DSM-5 (PCL-5). The PCL-5 gauged the presence and severity of PTSD-related symptoms and provided subscale scores that are matched to DSM-5 categories. This questionnaire was included to capture individual differences related to possible PTSD symptoms, which the PCL-5 as a screening and provisional measure is often used in similar research. As the overall PCL-5 scores did not indicate arousal or memory-driven findings in our non-clinical pilot, any impact of PTSD-related symptoms will not be discussed further.

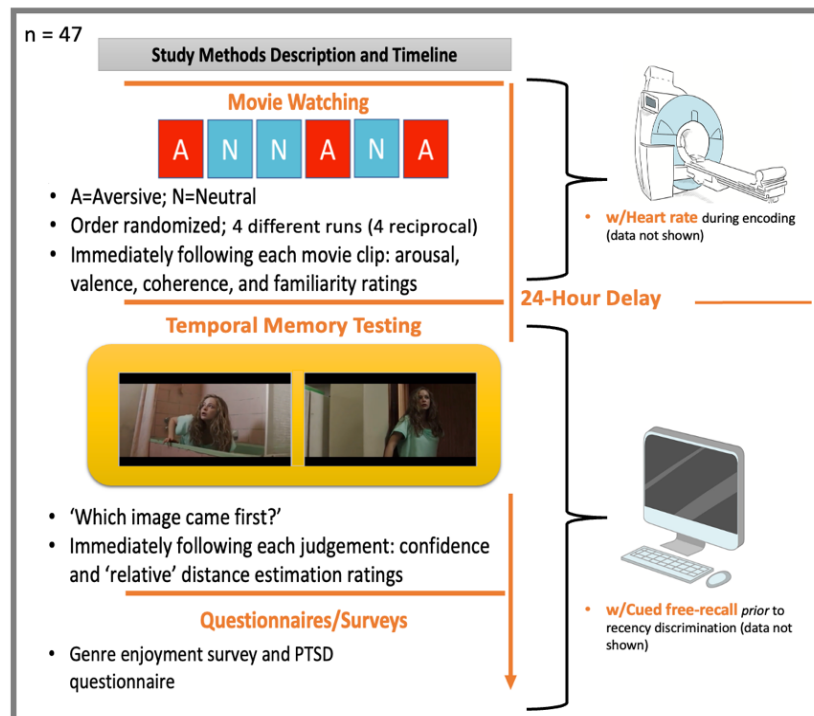


Figure 4: Overview of Methods Study 2. Overview of methods during encoding and memory test of fMRI, in-person Study 2.

### ***MRI Data Acquisition and Pre-processing***

MRI data was collected at the Temple University Brain Research & Imaging Center using a 3T Siemens Prisma scanner with a 20-channel parallel transmit-receive head coil. Functional whole brain blood oxygen-level dependent (BOLD) images were collected in a sagittal acquisition. During encoding, 77 brain volumes were collected in separate runs of each of the 13 blocks (6 movie clips and 7 resting fixation screens), each lasting for 120 seconds. We did not collect functional data during the within-encoding ratings. Participants completed the T1-weighted anatomic imaging, and then the fMRI study task, and finally, we collected field maps. T1-weighted images are used for co-registration.

We preprocessed our data with the standard fMRIPrep pipeline. DICOM images were converted to NIFTI format with Brain Imaging Data Structure nomenclature using dcm2niix (Li et al., 2016) and visually inspected for conversion errors and data exclusion criteria (e.g., signal drop-out from Falx calcification, anatomic abnormalities). Further quality control was achieved by manual inspection of structural and functional images for exclusions.

### ***Subject Level Estimations of Movie-level Response***

To estimate univariate activation, following preprocessing, a GLM for conditional movie clips was modeled with separate regressors and convolved with a double- $\gamma$  HRF as an event-related response, capturing a single extended trial for each run. Six head-motion parameters, their first derivatives, and time series extracted from CSF and white matter were added as covariates to the model to reduce noise (from the fMRIPrep output). The GLMs were then run using the fMRI Expert Analysis Tool as implemented in FSL. Beta-

parameters for the first level contrast of clip versus baseline were then extracted for each of our region(s) of interest (ROI(s)) and taken separately for each hemisphere.

To estimate functional connectivity, nodal time series were extracted as the mean aggregate time course across voxels in each region; Pearson's correlation measures the linear association between two variables. These time series represent the sequence of BOLD activation measurements after being concatenated together for each subject for each movie clip. To characterize functional connectivity, we ran a PPI analysis using a GLM with the four regressors derived from our univariate analysis as our psychological regressors and the neural data as the physiological regressor (i.e., seed ROI and target ROI) and then multiplied these factors to generate PPI regressors, which will generate beta values to test our hypotheses for functional coupling between ROI seed and ROI targets.

### ***Brain Regions of Interest***

After carefully considering the animal literature, we understood that although many brain areas beyond the MTL may be involved during the study, the primary areas of interest are the amygdala, hippocampus, and cortical MTL. While we may not capture the full range of memory during threat-related arousal movie watching, these are brain areas in threat models across species and studies, with remaining questions even at the level of sub-cortical structures.

The hippocampal ROIs were taken from the Harvard-Oxford subcortical atlas and thresholded at 50%. We then segmented the hippocampus laterally and into thirds and used the anterior hippocampus and posterior hippocampus separately for ROI analyses. The left and right perirhinal cortex masks were created from manually segmented T1

images and thresholded at 50% (using publicly available resources from the MemoLab (PI: Ritchey), see ‘Data and code’ <http://www.thememolab.org/resources/>). Sub-nuclei of the amygdala ROIs were taken from subdivision boundaries obtained from the Juelich histological atlas based on available probabilistic maps (Amunts et al., 2005). These ROIs were defined at the group and resampled from standard to native space using FLIRT and transformation matrices. Functional beta maps were projected from native to MNI space using FLIRT transformations and activities were extracted from ROIs using FSL tools, enabling further statistical analysis.

The primary neural analyses focused on univariate signals and functional connectivity amongst MTL regions of interest (ROIs). These ROIs included the sub-nuclei of the amygdala central-medial amygdala and basolateral amygdala, anterior cortical-MTL (perirhinal cortex), and hippocampus (anterior hippocampus, posterior hippocampus). Generally, we were looking for differential activation that varies as a function of arousal and/or valence during encoding and any possible downstream effects captured at the memory test. To do so, we extracted beta-weights from a contrast of clip versus baseline for each run of the task. The ROIs for Study 2 have been identified in both animal and human literature as threat-related networks, although the perirhinal cortex has been less studied compared with the hippocampus (Gregory et al., 2020).

### ***Statistical Analysis***

Statistical analyses, including multilevel modeling and regression, were conducted using R (see Study 1 above for details on R packages). Our analysis of behavioral data was identical to Study 1. All predictor variables scores were again mean-centered before analyses. This included within-encoding ratings (arousal, valence),

univariate data, and functional connectivity data. Significance was determined by a p-value  $< 0.05$  and the significance of individual dependent variables was assessed with the `lmerTest` package. Interaction findings were then further investigated with the `interaction` package in R (<https://www.rdocumentation.org/packages/interactions/versions/1.1.5>), using ‘`probe_interactions`’, ‘`sim_slopes`’ and ‘`johnson_newman`’ functions to explore statistical regressions and visualization.

### ***Variables***

The main independent variable across these studies is threat-related arousal, collapsed across both categories of aversive and neutral movie clips. There are several behavioral and neural dependent variables. The main behavioral measures are time (recency discrimination of order accuracy) and distance (temporal estimations of relative expanse or constriction). Confidence measures and individual difference ratings were outside the scope of this analysis.

The neural measure will be the BOLD signal in our ROIs for both univariate activation for each clip, as well as functional connectivity between sub-regions of the amygdala with the anterior hippocampus, posterior hippocampus, and perirhinal cortex for each clip. Laterality was added to the models as an interaction term to test whether the effects were specific to the right or left hemisphere.

### ***Approach to Arousal in Neural Analyses***

To determine if an ROI predicted recency discrimination as a main effect, we used a model comparison of:

- Baseline model: Recency discrimination  $\sim 1 + \text{arousal} + \text{laterality} + (1|\text{PID}) + (1|\text{movie})$

- Target model: Recency discrimination  $\sim$  ROI (or seed-ROI to target-ROI) + arousal + laterality + (1|PID) + (1|movie)

ROI models interacted with arousal to predict recency discrimination, used:

- Baseline model: Recency discrimination  $\sim$  ROI (or seed-ROI to target-ROI) + arousal + laterality + (1|PID) + (1|movie)
- Target model: Recency discrimination  $\sim$  ROI (or seed-ROI to target-ROI) \* arousal + laterality + (1|PID) + (1|movie)

ROI models interacted with laterality to predict recency discrimination, used:

- Baseline model: Recency discrimination  $\sim$  ROI (or seed-ROI to target-ROI) + laterality + arousal + (1|PID) + (1|movie)
- Target model: Recency discrimination  $\sim$  ROI (or seed-ROI to target-ROI) \* laterality + arousal + (1|PID) + (1|movie)

ROI models interacted with both arousal and laterality, used:

- Baseline model: Recency discrimination  $\sim$  1 + ROI (or seed-ROI to target-ROI) + arousal + laterality + (1|PID) + (1|movie)
- Target model: Recency discrimination  $\sim$  (ROI (or seed-ROI to target-ROI) \* arousal \* laterality) + ROI (or seed-ROI to target-ROI) + arousal + laterality + (1|PID) + (1|movie)

All functional connectivity models followed the same format as above.

For distance estimation, again we followed the models as above except for adding the error term of movie order ('movieRun') as it was found to be significant only for this measure.

## CHAPTER 3

### REGENCY DISCRIMINATION AND NEUROBEHAVIORAL MARKERS OF THREAT-RELATED AROUSAL

Our methodological approach was developed to test our model of neural mechanisms of threat-related arousal on temporal memory. Here, in Chapter 3 we characterize our temporal memory measure of recency discrimination during Study 1 (behavioral only) and Study 2 (behavior + fMRI). During encoding, participants did not know the type of information to prioritize, and thus the temporal order memory at the test opened a window into how participants organized and searched their memory. They may use spatial cues and specific details separately to represent how the encoded event unfolds, but they may also use the sequential nature of these details and events in concert. We may not have a method to directly test this, but with the background presented in Chapter 1, temporal order memory of within-encoded events may help to delve further into the isolated or combined use of these strategies. Recency discrimination has been used to query temporal order memory in many animal (Blumberg, 2015) and human studies (Bangert et al., 2019; Lositsky et al., 2016; Manning et al., 2011; Wen & Egner, 2022). Here, we explore recency discrimination across the hippocampus and perirhinal cortex, as past research has detailed a role for the MTL during encoding for successful temporal order memory (see review, Clewett et al., 2019).

Notably, recency discrimination queries temporal order in a way that produces a specific correct answer, unlike distance estimation (see Chapter 4), which offers a more subjective assessment. As such, the recency discrimination task in our study required participants to make an objective decision that relied on analyzing a still image to

determine the temporal order of the encoded movie clip using only clues from still images presented at the memory test.

If our threat-related arousal encoding study supports our past research, we hypothesize that arousal-related brain areas (i.e., amygdala) will predict better temporal order memory performance as queried by recency discrimination in the hippocampus and perirhinal cortex.

### **Recency Discrimination Analyses Overview**

For all recency discrimination models, we are interested in understanding how arousal impacts temporal memory order. As recency discrimination relies on the event structure of the entire movie clip and details of still images to guide memory, we predicted an increase of activity in and between ROIs relating to narrative elements of the threat-related movie clips, particularly under high arousal, with a specific focus on interactions of the central-medial and basolateral amygdala with the anterior hippocampus. First, I will present our behavioral findings from Study 1, and then present behavioral, univariate, and functional connectivity analyses from Study 2.

### **Results Study 1**

#### ***Behavioral Findings***

**Does Arousal or Valence Predict Temporal Memory Order at Immediate Test?** We first wanted to test the influence of threat-related arousal on recency discrimination behaviorally, using an online version of our study including an immediate test. Here, we modeled within-encoding arousal ratings to predict performance on recency discrimination, collapsed across aversive and neutral conditions. As predicted, we found that higher arousal ratings were associated with better recency discrimination

(tm: recency discrimination  $\sim$  arousal + laterality + (1|PID) + (1|movie); bm: recency discrimination  $\sim$  1 + laterality + (1|PID) + (1|movie);  $\chi^2(1) = 19.578$ ,  $\beta = 0.01$ , SE = 0.004,  $p < 0.001$ ; tm AIC: -28.654, bm AIC: -11.019; Figure 5).

We next wanted to determine if valence added explanatory power to our models, and when including valence in our model we found that it did not have any additional significant predictive power (tm: recency discrimination  $\sim$  valence + arousal + laterality + (1|PID) + (1|movie); bm: recency discrimination  $\sim$  arousal + laterality + (1|PID) + (1|movie);  $\chi^2(1) = 0.117$ ,  $\beta = -0.0003$ , SE = 0.0008,  $p = 0.7324$ ; tm AIC: -26.764, bm AIC: -28.654).

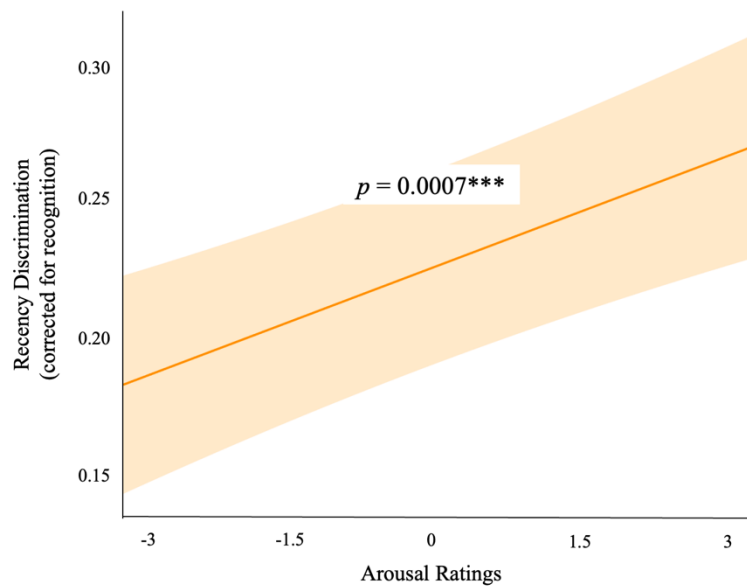


Figure 5: Arousal Ratings in Recency Discrimination at Immediate Test. Higher arousal predicted better recency discrimination performance at immediate memory test.

## Study 1 Results Discussion

In all, our behavioral findings utilizing an immediate memory test confirmed our prediction that arousal was significantly related to recency discrimination, supporting the value of studying these processes during the scanning of the brain.

We found that arousal ratings led to a better recency discrimination measure regardless of the condition of the movie clip. Although this helps to disassociate arousal and valence (Table 1), it does not clarify which neural systems are engaged in threat-related arousal during objective judgments of events within an episode to determine temporal memory. As such, we behaviorally show arousal effects using our methodology, which will inform our intent to find neural mechanisms supporting threat-related arousal on temporal memory. Given valence did not show any significant effect as a variable, nor improve the arousal model, this variable will not be investigated further in subsequent analyses for this study.

Table 1. Behavioral recency discrimination models at immediate test (best-fit models in gray highlight/white text)

Within-encoding models	$\chi^2$	$\beta$	$SE$	p-value
Arousal model	19.6340	0.0200	0.0045	0.0000
Valence + arousal model	0.1100	-0.0028	0.0084	0.7401

## Results Study 2

### *Behavioral Findings*

#### **Does Arousal or Valence Predict Temporal Memory Order at Delay Test?.**

Adapting our study to an in-person fMRI version allowed us to characterize the influence of different brain regions on 24-hour recency discrimination memory, and any interacting effects of arousal. While we predicted that the arousal ratings would predict recency discrimination when testing temporal memory at delay, we did not find a behavioral relationship between memory and arousal in this Study 2 (tm: recency discrimination  $\sim$  arousal + laterality + (1|PID) + (1|movie); bm: recency discrimination  $\sim$  1 + laterality + (1|PID) + (1|movie);  $\chi^2(1) = 0.23$ ,  $\beta = -0.0001$ ,  $SE = 0.0003$ ,  $p = 0.6300$ ; tm AIC: -26.764, bm AIC: -28.654; Figure 6).

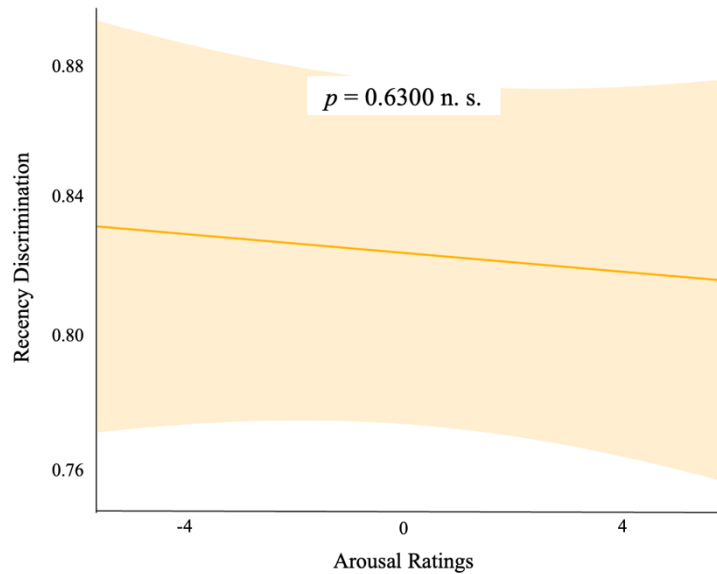


Figure 6: Arousal Ratings in Recency Discrimination at Delay Test. Arousal ratings were not predictive of recency discrimination performance at delay memory test.

Adding valence to this model did not increase model fit (tm: recency discrimination  $\sim$  valence + arousal + laterality + (1|PID) + (1|movie); bm: recency discrimination  $\sim$  1 + arousal + laterality + (1|PID) + (1|movie);  $\chi^2(1) = 0.6344$ ,  $\beta = 0.0005$ ,  $SE = 0.0006$ ,  $p = 0.4258$ ; tm AIC: -26.764, bm AIC: -28.654).

While we did not see that within-encoding ratings of arousal were related to our delay memory test, we believe that performing our study during fMRI and adding a 24-hour delay may explain this difference from Study 1. The first explaining arousal levels may have been elevated due to the nature of an fMRI scan, which may have been a factor of behavior not relating to memory at 24 hours. Further, consolidation factors between immediate and 24-hour later study may later memory/behavior profiles. Despite not finding a significant role of arousal on recency discrimination at the group level in Study 2 (Table 2), we were still interested in examining whether neural signatures captured variability in our memory findings. We theorized that while behavior may have been less clear, encoding mechanisms of the brain may be more apparent using our methodology as it relies less on self-report, and more on the natural unfolding of experience which we planned to study in our methodological design.

Table 2. Behavioral recency discrimination models at delay test

Within-encoding models	$\chi^2$	$\beta$	$SE$	p-value
Arousal model	0.2320	-0.0013	0.0028	0.6300
Valence + arousal model	0.6344	0.0045	0.0057	0.4258

## Univariate Findings

**Does Univariate ROI Activity Predict Temporal Memory Order?.** A model including univariate ROI activity of posterior hippocampus, compared with a baseline model, showed a marginal effect of better recency discrimination as activity increases (tm: recency discrimination  $\sim$  pHIP + arousal + laterality + (1|PID) + (1|movie); bm: recency discrimination  $\sim$  1 + arousal + laterality + (1|PID) + (1|movie);  $\chi^2(1) = 3.55$ ,  $\beta = 0.02$ , SE = 0.01,  $p = 0.06$ ; AIC tm: -214.69, AIC bm: -213.14; Figure 7).

No other univariate ROIs were significant or exhibited a trend towards significance for a main effect of ROI (Table 3). Further, univariate activity did not show an interaction of ROI by arousal, ROI by hemisphere, or 3-way interaction across activity, ROI, and laterality to predict recency discrimination (Table 3).

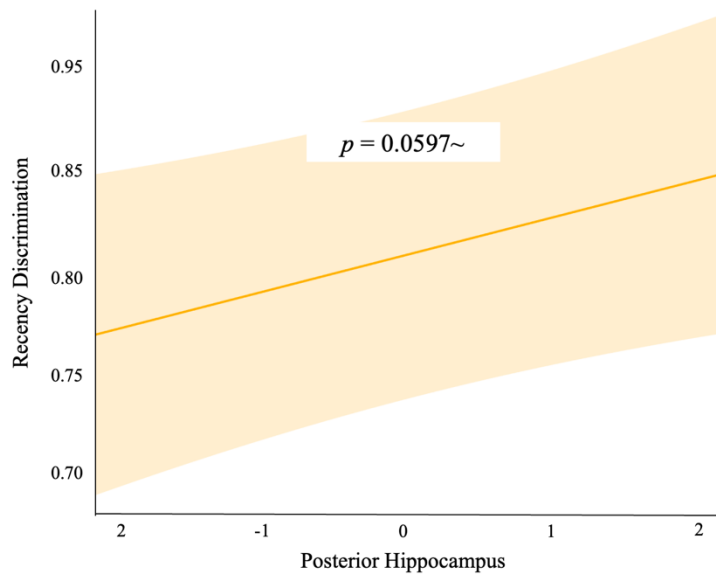


Figure 7: Univariate Posterior Hippocampus in Recency Discrimination. Temporal memory was predicted by increased posterior hippocampus univariate activity.

Table 3. Univariate model comparisons of recency discrimination (best-fit models in gray highlight/white text)

Basolateral amygdala models		$\chi^2$	$\beta$	<i>SE</i>	p-value
	BLA: non-interaction	0.1851	0.0066	0.0152	0.6670
	BLA: interaction with arousal	2.6929	0.0095	0.0058	0.1008
	BLA: interaction with hemisphere	0.1071	-0.0098	0.0301	0.7435
	BLA: interaction with arousal/hemisphere	0.0165	0.0014	0.0111	0.8978
Central-medial amygdala models		$\chi^2$	$\beta$	<i>SE</i>	p-value
	CEM: non-interaction	0.0002	0.0002	0.0110	0.9875
	CEM: interaction with arousal	0.0672	0.0010	0.0040	0.7955
	CEM: interaction with hemisphere	0.0263	-0.0035	0.0216	0.8713
	CEM: interaction with arousal/hemisphere	0.1938	0.0035	0.0079	0.6598
Anterior hippocampus models		$\chi^2$	$\beta$	<i>SE</i>	p-value
	Anterior-HPC: non-interaction	1.1805	0.0140	0.0129	0.2772
	Anterior-HPC: interaction with arousal	0.4177	0.0032	0.0050	0.5181
	Anterior-HPC: interaction with hemisphere	0.2771	0.0135	0.0256	0.5986
	Anterior-HPC: interaction with arousal/hemisphere	0.2626	-0.0048	0.0094	0.6083
Posterior hippocampus models		$\chi^2$	$\beta$	<i>SE</i>	p-value
	Posterior-HPC: non-interaction	3.5467	0.0237	0.0126	0.0597
	Posterior-HPC: interaction with arousal	1.3810	-0.0057	0.0048	0.2399
	Posterior-HPC: interaction with hemisphere	0.5760	-0.0188	0.0248	0.4479
	Posterior-HPC: interaction with arousal/hemisphere	0.1589	-0.0037	0.0092	0.6901

Table 3. (continued)

Perirhinal Cortex models	$\chi^2$	$\beta$	$SE$	p-value
PRC: non-interaction	0.3354	0.0075	0.0129	0.5625
PRC: interaction with arousal	1.7601	0.0064	0.0048	0.1846
PRC: interaction with hemisphere	0.0513	-0.0058	0.0258	0.8208
PRC: interaction with arousal/hemisphere	0.0000	0.0000	0.0093	0.9989

### ***Functional Connectivity Findings***

**Does Amygdala-to-Hippocampus Coupling Predict the Temporal Order of Events?** An interaction model including coupling of central-medial amygdala to anterior hippocampus with laterality, compared with a baseline model, showed a significant effect of interaction such that increased functional coupling was associated with better recency discrimination (tm: recency discrimination  $\sim$  CEM-aHIP \* laterality + arousal + (1|PID) + (1|movie); bm: recency discrimination  $\sim$  CEM-aHIP + arousal + laterality + (1|PID) + (1|movie);  $\chi^2(1) = 3.96$ ,  $\beta = -0.02$ ,  $SE = 0.01$ ,  $p < 0.05$ ; AIC tm: -216.44, AIC bm: -214.49; Figure 8). A fixed effect slope analysis of coupling of central-medial amygdala to anterior hippocampus interaction with laterality determined a significant slope in the left hemisphere ( $\beta = 0.22$ ,  $SE = 0.08$ ,  $t = 2.72$ ,  $p = 0.01$ ; Figure 8), but not the right hemisphere ( $p = 0.99$ ; Figure 8).

There was no other main effect of amygdala to hippocampus functional connectivity (Table 4). Further, there was no significant amygdala-to-hippocampus coupling by arousal, hemisphere, or both arousal and laterality 3-way interaction to predict recency discrimination (Table 4).

Table 4: Functional connectivity model comparisons of recency discrimination (best-fit models in gray highlight/white text)

Basolateral amygdala to anterior hippocampus		$\chi^2$	$\beta$	$SE$	p-value
	BLA to anterior-HPC: non-interaction	0.0718	-0.0166	0.0619	0.7887
	BLA to anterior-HPC: interaction with arousal	0.2007	-0.0097	0.0217	0.6541
	BLA to anterior-HPC: interaction with hemisphere	1.8039	-0.1648	0.1226	0.1792
	BLA to anterior-HPC: interaction with arousal/hemisphere	0.3343	-0.0243	0.0420	0.5631
Basolateral amygdala to posterior hippocampus		$\chi^2$	$\beta$	$SE$	p-value
	BLA to posterior-HPC: non-interaction	1.2776	0.0000	0.0157	0.2584
	BLA to posterior-HPC: interaction with arousal	0.3299	-0.0117	0.0203	0.5657
	BLA to posterior-HPC: interaction with hemisphere	0.0929	-0.0329	0.1080	0.7605
	BLA to posterior-HPC: interaction with arousal/hemisphere	0.0208	-0.0057	0.0398	0.8853
Central-medial amygdala to anterior hippocampus		$\chi^2$	$\beta$	$SE$	p-value
	CEM to anterior-HPC: non-interaction	3.3482	0.1019	0.0555	0.0673
	CEM to anterior-HPC: interaction with arousal	0.0063	0.0016	0.0196	0.9369
	CEM to anterior-HPC: interaction with hemisphere	3.9552	-0.2197	0.1102	0.0467
	CEM to anterior-HPC: interaction with arousal/hemisphere	2.3804	-0.0601	0.0389	0.1229

Table 4. (continued)

Central-medial amygdala to posterior hippocampus	$\chi^2$	$\beta$	$SE$	p-value
CEM to posterior-HPC: non-interaction	0.0001	-0.0004	0.0062	0.9937
CEM to posterior-HPC: interaction with arousal	1.5368	0.0261	0.0210	0.2151
CEM to posterior-HPC: interaction with hemisphere	0.1814	-0.0473	0.1111	0.6702
CEM to posterior-HPC: interaction with arousal/hemisphere	0.0002	-0.0006	0.0406	0.9880

**Does Amygdala-to-Cortical-MTL Coupling Predict the Temporal Order of Events?** We did not find any amygdala to perirhinal cortex functional connectivity findings to be significant nor show a trend towards significance for a main effect of functional coupling (Table 5). Furthermore, the functional connectivity of the amygdala to the perirhinal cortex did not show an interaction with ROI coupling by arousal, ROI coupling by hemisphere, or ROI coupling by arousal by laterality 3-way interaction to predict recency discrimination (Table 5).

Table 5. Functional connectivity model comparisons of recency discrimination

Basolateral amygdala to perirhinal cortex	$\chi^2$	$\beta$	$SE$	p-value
BLA to PRC: non-interaction	1.2167	-0.0572	0.0518	0.2700
BLA to PRC: interaction with arousal	0.0027	0.0010	0.0198	0.9586
BLA to PRC: interaction with hemisphere	3.5863	-0.1941	0.1023	0.0583
BLA to PRC: interaction with arousal/hemisphere	0.0474	-0.0083	0.0381	0.8277

Table 5. (continued)

Central-medial amygdala to perirhinal cortex	$\chi^2$	$\beta$	<i>SE</i>	p-value
CEM to PRC: non-interaction	0.0014	-0.0019	0.0500	0.9705
CEM to PRC: interaction with arousal	2.9795	-0.0322	0.0186	0.0843
CEM to PRC: interaction with hemisphere	1.3904	0.1186	0.1004	0.2383
CEM to PRC: interaction with arousal/hemisphere	0.3169	-0.0207	0.0368	0.5735

## Study 2 Results Discussion

In full, Study 1 and Study 2 using recency discrimination when examining temporal order memory following threat-related arousal encoding did provide evidence for behavioral enhancements on immediate memory but not after a delay. Neural findings did not confirm our brain-related arousal model of memory (see Figure 9). In sum, our univariate finding of the posterior hippocampus and our functional connectivity findings between the central-medial amygdala to anterior hippocampus showed better performance of recency discrimination, but we did not find any interactions of arousal.

In investigating how these findings are overall impacted by the temporal order of events, while we did not see our behavioral findings lasting to a 24-hour delay test, we believe the within-encoding rating of arousal may have been influenced by an artificial ‘threat of scanner’ that may have increased attentional factors, especially during neutral movie watching. However, we did see better memory performance in areas of the brain known to be important for threat-related arousal and temporal-order memory. This gives

us support but does not confirm these regions do indeed underlie the structure of threat-related arousal memory.

As mentioned previously, if this is a measure of *what happened*, then participants must use the information given to them (details of still images) and construct the entire scope of the episodic scene (global information) to best perform using temporal order memory. Without the use of arousal-driven landmarks in the still images, a full recollection of the episodic memory may be necessary to make an objective decision. This global memory recollection, using fine-grained details to determine the time when salient events happen, does not need to answer the question of *how it happened*. As such, having a separate memory measure that may be built upon item-related memory, using fine-grained details to support global recollection, gave us a subjective measure in our study. Accordingly, in Chapter 4 we will examine distance estimation as a measure in contrast to recency discrimination to better determine the factors of our threat-related arousal encoding paradigm.

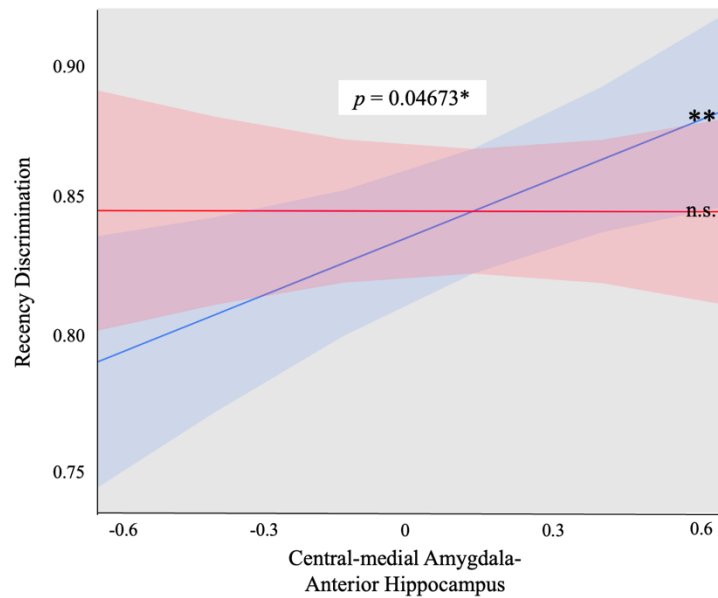


Figure 8: Functional Connectivity of Basolateral Amygdala-Anterior Hippocampus in Recency Discrimination. Temporal distance was predicted by basolateral amygdala to anterior hippocampus functional coupling during interaction with arousal (blue, left hemisphere; red, right hemisphere).

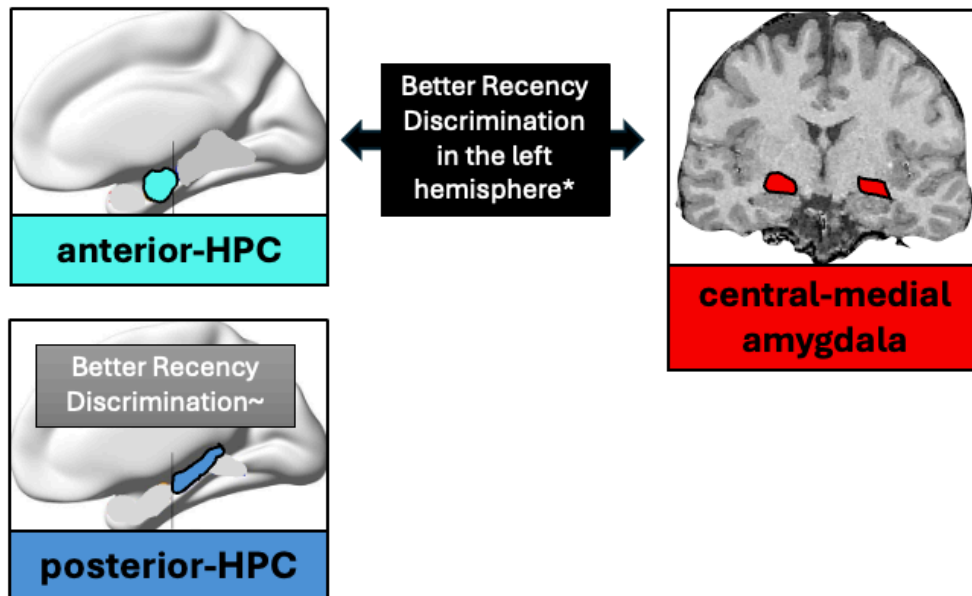


Figure 9: Summary of Recency Discrimination Findings in Study 2.  
 Univariate: posterior hippocampus shows a trend predicting better recency discrimination as activity increases, without interactions. Functional coupling: central-medial amygdala to anterior hippocampus coupling significantly interacts with laterality, showing better recency discrimination as left hemisphere coupling is more in-synch. All models tested at a significant at  $p < 0.05$ .

## CHAPTER 4

### DISTANCE ESTIMATION AND NEUROBEHAVIORAL MARKERS OF THREAT-RELATED AROUSAL

Here, in Chapter 4 we characterize our temporal memory measure of distance estimation during Study 1 (behavioral only) and Study 2 (behavior + fMRI). Distance estimation can be roughly defined as how a past episode, when recollected, differs in the retroactive estimation of elapsed time or deviates in structure as to when events happened from the actual encoded event. This focus is less used in practice, but concerning our measure of recency discrimination, it allows for a subjective measure of episodic memory to better understand how temporal order memory is manipulated in behavioral and neural threat-related arousal.

For this measure, participants were unaware that still images were derived and paired in a precise systemic technique (see Chapters 2 and 3), such that the actual distance of all the images was the same length of time between still images. Then when asked for a distance estimation as a relative question with an arbitrary answer, but with the time distance kept static across movie clips and still images, any bias from a consistent answer of the four options (very close, close, far, very far), represents a variation in memory. Importantly cortical-MTL has been theorized as vital for item memory (Davachi, 2006; Goyal et al., 2020; Kirwan & Stark, 2004; Rugg et al., 2012) and associative memory (Awipi & Davachi, 2008), as described in Chapter 3 may be important factors in temporal memory. Although we may again not have the methodology to describe item-based vs associate strategies, it may help within the framework of gist-level encoding vs fine-grained detail-level encoding.

Following this line of work, our use of distance estimation is designed for this level of subjectivity using ‘very close’, ‘close’, ‘far’, and ‘very far’ did not follow an exact scale that is measurable. As such, we used this relative measure (developed using specific procedural elements, see Chapter 2) of episodic encoding of elapsed time in retrospective recollection. A large body of work in the field has used distance estimation more objectively, asking participants to give the full episode an entire retrospective decision about how long stimuli are presented in minutes/seconds (Palombo & Verfaellie, 2017; Petrucci et al., 2024). Here we followed the Davachi group’s use of distance estimation but will discuss our results regarding these differences in Chapter 5. Finally, as with recency discrimination, there is a chance that distance estimation may recruit hippocampal areas to better contain information for narrative elements at both global and fine-grained levels, which could stem from arousal differences in the amygdala-related bias of MTL. Having two measures that are designed to have both an objective, true answer (recency discrimination) and another for a subjective, relative answer (distance estimation) helps to bolster our findings.

If our threat-related arousal encoding study supports our past research highlighting temporal memory benefits following arousal experience, we hypothesize that arousal-related brain areas (amygdala) will predict a compression of elapsed time as queried by distance estimation in the hippocampus and perirhinal cortex.

### **Distance Estimations Analyses Overview**

For all distance estimation models, we were interested in understanding how arousal impacts temporal memory order. Distance estimation may rely more heavily on fine-grained detailed or more gist-like detail memories to guide recollection, for which

we do not have specific predictions. It may be that an increase of activity in and between ROIs relating to item-based elements of the threat-related movie clips, particularly under high arousal. As a model specifically again focusing on interactions of the central-medial and basolateral amygdala with the anterior hippocampus, as well as central-medial amygdala to cortical-MTL, we may then predict that item-based strategies are more relied upon than spatial-based strategies during encoding. First, I will present our behavioral findings from Study 1, and then present behavioral, univariate, and functional connectivity analyses from Study 2.

## **Results Study 1**

### ***Behavioral Findings***

**Does Arousal or Valence Predict the Estimation of Elapsed Time at Immediate Test?.** We again first wanted to test the influence of threat-related arousal on distance estimation in Study 1 at immediate test. Here, we modeled within-encoding arousal ratings to predict compression or expansion of distance estimation, collapsed across aversive and neutral conditions. As predicted, higher arousal ratings were associated with compressed distance estimation (tm: distance estimation ~ arousal + laterality + movieRun + (1|PID) + (1|movie); bm: distance estimation ~ 1 + laterality + movieRun + (1|PID) + (1|movie);  $\chi^2(1) = 6.4927$ ,  $\beta = 0.02$ ,  $SE = 0.007$ ,  $p < 0.05$ ; tm AIC: 1840.6, bm AIC: 1845.1; Figure 10).

We next wanted to determine if valence added explanatory power to our models, and when including valence in our model we found that it did not have any additional significant predictive power (tm: distance estimation ~ valence + arousal + Laterality + movieRun + (1|PID) + (1|movie); bm: distance estimation ~ 1 + arousal + Laterality +

movieRun + (1|PID) + (1|movie);  $\chi^2(1) = 0.0004$ ,  $\beta = -0.0003$ ,  $SE = 0.01$ ,  $p = 0.9839$ ;  
tm AIC: 1842.6, bm AIC: 1840.6).

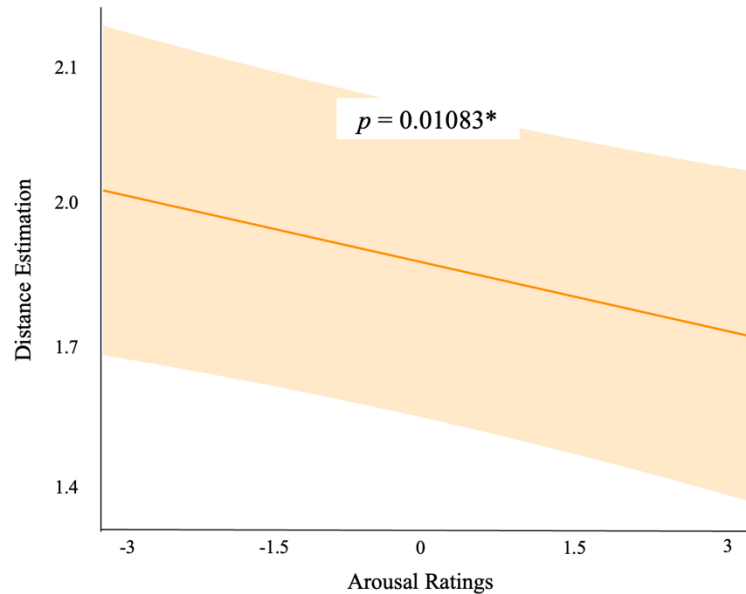


Figure 10: Arousal Ratings in Distance Estimation at Immediate Test. Higher arousal predicted compressed distance estimation ratings at immediate memory test.

### Study 1 Results Discussion

In all, our behavioral findings utilizing an immediate memory test confirm our prediction that arousal was significantly related to distance estimation, which supported studying these processes during the scanning of the brain.

We again found that arousal ratings predicted our temporal order measure, this time demonstrated through the compression of distance estimation measure regardless of the condition of the movie clip. Although this further helps to disassociate arousal and valence (Table 6), it is still unknown which neural systems are engaged in threat-related arousal during subjective perception of elapsed time within an episode to determine

temporal memory. Given the lack of explanatory effects of valence, we have again removed it from subsequent analyses.

Table 6. Behavioral distance estimation models at immediate test (best-fit models in gray highlight/white text)

Within-encoding models	$\chi^2$	$\beta$	SE	p-value
Arousal model	6.493	-0.019	0.007	0.011
Valence + arousal model	0.000	0.000	0.014	0.984

## Results Study 2

### *Behavioral Findings*

#### **Does Arousal or Valence Predict the Estimation of Elapsed Time at Delay**

**Test?** Adapting our study to an in-person fMRI version again allowed us to characterize the influence of different brain regions on 24-hour distance estimation memory, and any interacting effects of arousal. While we predicted that the arousal ratings would predict distance estimation at a delay, we did not find a behavioral relationship between distance memory and arousal in Study 2 (tm: distance estimation ~ arousal + laterality + movieRun + (1|PID) + (1|movie); bm: distance estimation ~ 1 + laterality + movieRun + (1|PID) + (1|movie);  $\chi^2(1) = 0.2309$ ,  $\beta = 0.003$ , SE = 0.005,  $p = 0.6309$ ; tm AIC: 491.73, bm AIC: 489.96; Figure 11).

Adding valence to this model did not increase model fit (tm: distance estimation ~ valence + arousal + Laterality + movieRun + (1|PID) + (1|movie); bm: distance

estimation  $\sim 1 + \text{arousal} + \text{Laterality} + \text{movieRun} + (1|\text{PID}) + (1|\text{movie})$ ;  $\chi^2(1) = 2.0656$ ,  $\beta = 0.15$ ,  $SE = 0.01$ ,  $p = 0.1507$ ; tm AIC: 491.66, bm AIC: 491.73).

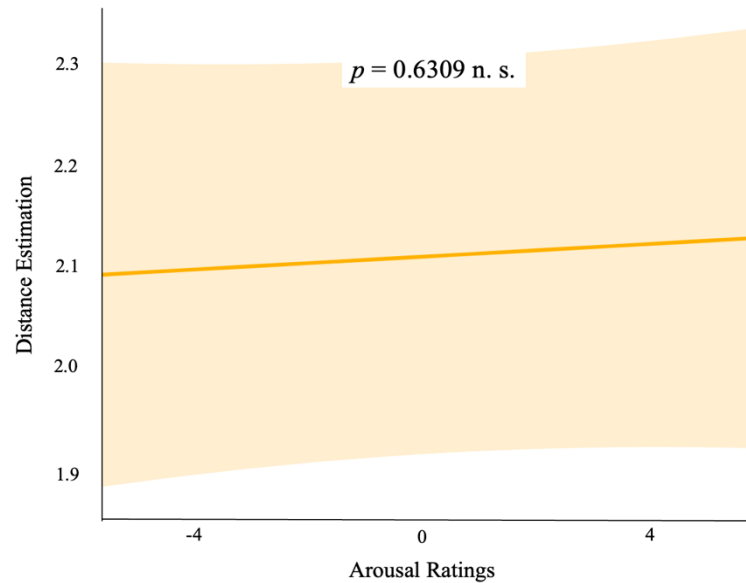


Figure 11: Arousal Ratings in Distance Estimations during Delay Test. Higher arousal was not predictive of distance estimation ratings at delay memory test.

Again we did not see within-encoding ratings of arousal at the delay memory test, see Chapter 3 and limitations in Chapter 5 (Table 7).

Table 7. Behavioral distance estimation models at delay test

Within-encoding models	$\chi^2$	$\beta$	$SE$	p-value
Arousal model	0.231	0.003	0.005	0.631
Valence + arousal model	2.066	0.015	0.011	0.151

## Univariate Findings

### Does Univariate ROI Activity Predict the Estimation of Elapsed Time?. A

model including univariate ROI activity of perirhinal cortex, compared with a baseline model, showed a significant effect of compression of distance estimation as activity

increases (tm: distance estimation  $\sim$  PRC + arousal + laterality + (1|PID) + (1|movie);

bm: distance estimation  $\sim$  1 + arousal + laterality + (1|PID) + (1|movie);  $\chi^2(1) = 5.12$ ,  $\beta$

$= 0.05$ ,  $SE = 0.02$ ,  $p < 0.05$ ; AIC tm: 490.61, AIC bm: 493.73; Figure 12.

No other univariate ROIs were significant nor showed a trend towards

significance for a main effect of ROI (Table 8). Further, univariate activity did not show

an interaction of ROI by arousal, ROI by hemisphere, or 3-way interaction across

activity, ROI, and laterality to predict distance estimation (Table 8).

Table 8. Univariate model comparisons of distance estimation (best-fit models in gray highlight/white text)

Basolateral amygdala models		$\chi^2$	$\beta$	$SE$	p-value
	BLA: non-interaction	0.4816	0.0197	0.0284	0.4877
	BLA: interaction with arousal	0.4174	0.0070	0.0109	0.5182
	BLA: interaction with hemisphere	0.4321	0.0366	0.0557	0.5110
	BLA: interaction with arousal/hemisphere	0.6022	-0.0161	0.0207	0.4377
Central-medial amygdala models		$\chi^2$	$\beta$	$SE$	p-value
	CEM: non-interaction	0.3846	0.0127	0.0204	0.5351
	CEM: interaction with arousal	0.7684	0.0066	0.0076	0.3807
	CEM: interaction with hemisphere	1.1126	-0.0422	0.0400	0.2915
	CEM: interaction with arousal/hemisphere	0.1200	-0.0051	0.0146	0.7290

Table 8. (continued)

Anterior hippocampus models		$\chi^2$	$\beta$	<i>SE</i>	p-value
	Anterior-HPC: non-interaction	0.0189	0.0033	0.0241	0.8907
	Anterior-HPC: interaction with arousal	1.8691	-0.0128	0.0094	0.1716
	Anterior-HPC: interaction with hemisphere	0.1617	0.0191	0.0475	0.6876
	Anterior-HPC: interaction with arousal/hemisphere	0.3522	-0.0104	0.0175	0.5529
Posterior hippocampus models		$\chi^2$	$\beta$	<i>SE</i>	p-value
	Posterior-HPC: non-interaction	2.3642	0.0365	0.0237	0.1241
	Posterior-HPC: interaction with arousal	2.2469	-0.0138	0.0092	0.1339
	Posterior-HPC: interaction with hemisphere	0.1570	0.0183	0.0462	0.6919
	Posterior-HPC: interaction with arousal/hemisphere	0.1361	0.0063	0.0172	0.7122
Perirhinal cortex models		$\chi^2$	$\beta$	<i>SE</i>	p-value
	PRC: non-interaction	5.1200	0.0545	0.0240	0.0237
	PRC: interaction with arousal	0.0151	0.0011	0.0092	0.9022
	PRC: interaction with hemisphere	0.0001	-0.0004	0.0477	0.9935
	PRC: interaction with arousal/hemisphere	0.1297	-0.0062	0.0173	0.7187

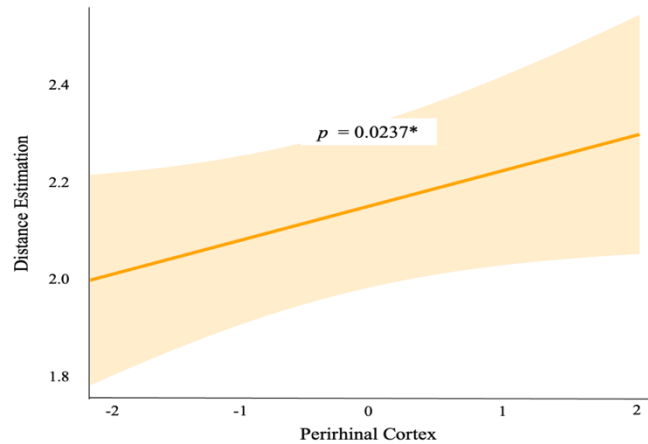


Figure 12: Univariate Perirhinal Cortex in Distance Estimation. Temporal distance was predicted by basolateral amygdala to posterior hippocampus functional coupling.

### ***Functional Connectivity Findings***

**Does Amygdala-to-Hippocampus Coupling Predict the Estimation of Elapsed Time?.** An interaction model including the coupling of basolateral amygdala to anterior hippocampus with arousal, compared with a baseline model, showed a significant effect of interaction such that increased functional coupling was associated with a compression of distance estimation dependent on the level of arousal (tm: distance estimation  $\sim$  BLA-aHIP \* arousal + laterality + (1|PID) + (1|movie) + (1|movieRun); bm: distance estimation  $\sim$  BLA-aHIP + arousal + laterality + (1|PID) + (1|movie) + (1|movieRun);  $\chi^2(1) = 5.77$ ,  $\beta = 0.10$ ,  $SE = 0.04$ ,  $p < 0.05$ ; AIC tm: 482.00, AIC bm: 485.77; Figure 13). A fixed effect slope analysis of coupling of basolateral amygdala to anterior hippocampus interaction with arousal determined a significant slope of compression at low ( $\beta = -0.65$ ,  $SE = 0.16$ ,  $t = -3.95$ ,  $p < 0.001$ ; Figure 13) to medium ( $\beta = -0.36$ ,  $SE = 0.11$ ,  $t = -3.18$ ,  $p < 0.001$ ; Figure 13) levels of arousal, but not at high levels of arousal ( $p = 0.63$ ; Figure 13).

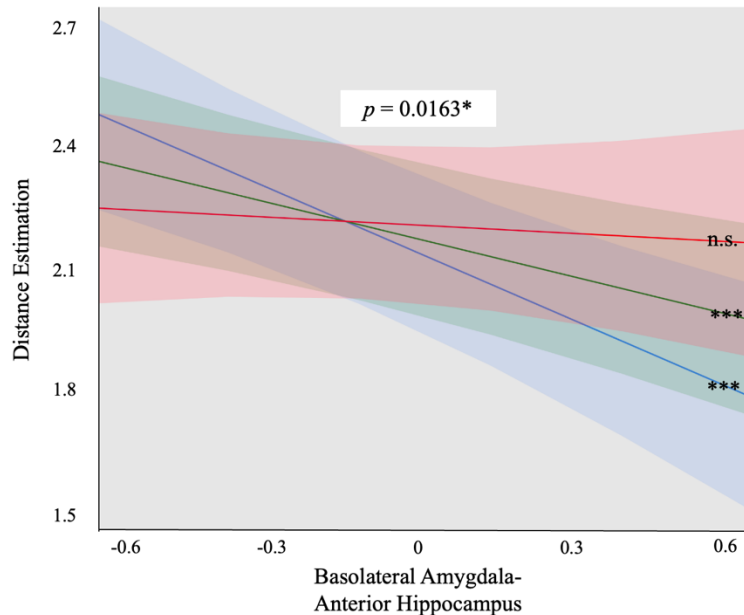


Figure 13: Functional Connectivity of Basolateral Amygdala-Anterior Hippocampus in Distance Estimation. Temporal distance was predicted by basolateral amygdala to anterior hippocampus functional coupling during interaction with arousal (blue, low arousal; green, medium arousal; red, high arousal).

A model including the coupling of basolateral amygdala to the posterior hippocampus, compared with a baseline model, showed a significant effect such that increased functional coupling was associated with compression of distance estimation irrespective of arousal (tm: distance estimation  $\sim$  BLA-pHIP + arousal + laterality + (1|PID) + (1|movie) + (1|movieRun); bm: distance estimation  $\sim$  1 + arousal + laterality + (1|PID) + (1|movie) + (1|movieRun);  $\chi^2(1) = 4.33$ ,  $\beta = -0.21$ ,  $SE = 0.10$ ,  $p < 0.05$ ; AIC tm: 491.40, AIC bm: 493.73; Figure 14).

An interaction model including the coupling of the central-medial amygdala to anterior hippocampus with arousal and hemispheric laterality, compared with a baseline

model, showed a significant effect of a triple interaction, such that increased functional coupling was associated with a compression of distance estimation at high arousal, but interestingly, an expansion of distance estimation at low arousal, all of which was found only in the right hemisphere (tm: distance estimation  $\sim$  (CEM-aHIP \* arousal \* laterality) + arousal + laterality + (1|PID) + (1|movie) + (1|movieRun); bm: distance estimation  $\sim$  (CEM-aHIP \* arousal) + (CEM-aHIP \* laterality) + (arousal \* laterality) + CEM-aHIP + arousal + laterality + (1|PID) + (1|movie) + (1|movieRun);  $\chi^2(1) = 4.78$ ,  $\beta = -0.16$ ,  $SE = 0.07$ ,  $p < 0.05$ ; AIC tm: 492.17, AIC bm: 494.95; Figure 15). A fixed effect slope analysis of coupling of the central-medial amygdala to the anterior hippocampus in the right hemisphere found that arousal was determined to a significant slope of compression at high levels of arousal ( $\beta = -0.46$ ,  $SE = 0.21$ ,  $t = -2.15$ ,  $p = 0.03$ ; Figure 15), and an expansion of distance estimation at low levels of arousal ( $\beta = 0.52$ ,  $SE = 0.19$ ,  $t = 2.70$ ,  $p = 0.01$ ; Figure 15), but not at medium levels of arousal ( $p = 0.82$ ; Figure 15).

Central-medial amygdala to posterior hippocampus functional connectivity findings were not significant nor showed a trend towards significance for a main effect of functional coupling (Table 9). Further, functional connectivity of the central-medial amygdala to the posterior hippocampus did not show an interaction with ROI coupling by arousal, ROI coupling by hemisphere, or ROI coupling by arousal by laterality 3-way interaction to predict distance estimation (Table 9).

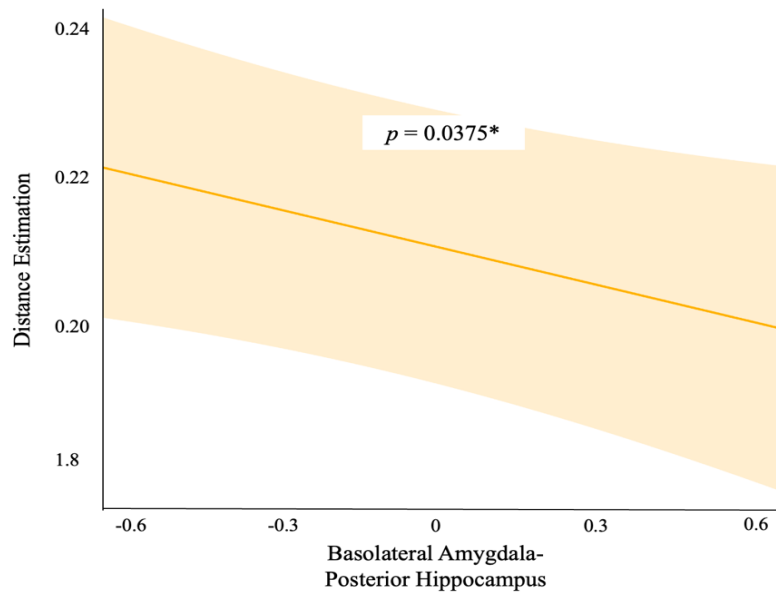


Figure 14: Functional Connectivity of Basolateral Amygdala-Posterior Hippocampus in Distance Estimation. Temporal distance was predicted by more in-sync basolateral amygdala-posterior hippocampus coupling.

Table 9. Functional connectivity model comparisons of distance estimation (best-fit models in gray highlight/white text)

Basolateral amygdala to anterior hippocampus		$\chi^2$	$\beta$	<i>SE</i>	p-value
	BLA to anterior-HPC: non-interaction	9.9604	-0.3646	0.1149	0.0016
	BLA to anterior-HPC: interaction with arousal	5.7687	0.0978	0.0405	0.0163
	BLA to anterior-HPC: interaction with hemisphere	0.0594	0.0552	0.2262	0.8075
	BLA to anterior-HPC: interaction with arousal/hemisphere	0.0456	-0.0165	0.0772	0.8309

Table 9. (continued)

Basolateral amygdala to posterior hippocampus		$\chi^2$	$\beta$	<i>SE</i>	p-value
	BLA to posterior-HPC: non-interaction	4.3271	-0.2127	0.1019	0.0375
	BLA to posterior-HPC: interaction with arousal	1.3960	-0.0453	0.0383	0.2374
	BLA to posterior-HPC: interaction with hemisphere	0.1301	0.0724	0.2006	0.7183
	BLA to posterior-HPC: interaction with arousal/hemisphere	0.4886	0.0518	0.0740	0.4845
Central-medial amygdala to anterior hippocampus		$\chi^2$	$\beta$	<i>SE</i>	p-value
	CEM to anterior-HPC: non-interaction	0.1290	0.0373	0.1039	0.7194
	CEM to anterior-HPC: interaction with arousal	6.5968	-0.0949	0.0368	0.0102
	CEM to anterior-HPC: interaction with hemisphere	0.1631	0.0836	0.2068	0.6863
	CEM to anterior-HPC: interaction with arousal/hemisphere	4.7806	-0.1595	0.0727	0.0288
Central-medial amygdala to posterior hippocampus		$\chi^2$	$\beta$	<i>SE</i>	p-value
	CEM to posterior-HPC: non-interaction	0.0745	-0.0288	0.1052	0.7849
	CEM to posterior-HPC: interaction with arousal	0.0081	-0.0036	0.0395	0.9281
	CEM to posterior-HPC: interaction with hemisphere	0.0908	-0.0624	0.2068	0.7632
	CEM to posterior-HPC: interaction with arousal/hemisphere	3.7585	-0.1470	0.0756	0.0525

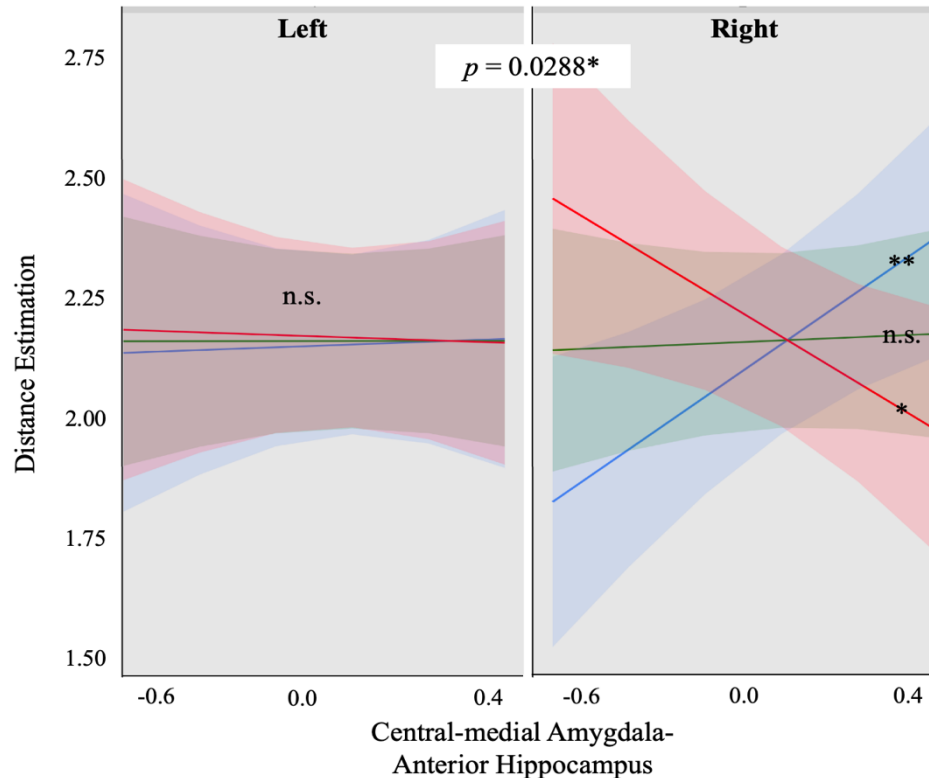


Figure 15: Functional Connectivity of Central-medial Amygdala-Anterior Hippocampus in Distance Estimation. Temporal distance was predicted by more in-sync central-medial amygdala-anterior hippocampus functional coupling during interaction with arousal and hemisphere (blue, low arousal; green, medium arousal; red, high arousal).

### Does Amygdala-to-Cortical-MTL Coupling Predict the Estimation of

**Elapsed Time?** An interaction model including the coupling of central-medial amygdala to perirhinal cortex with arousal, compared with a baseline model, showed a marginal effect of interaction such that increased functional coupling was associated with a compression of distance estimation (tm: distance estimation  $\sim$  CEM-PRC \* arousal + laterality + (1|PID) + (1|movie) + (1|movieRun); bm: distance estimation  $\sim$  CEM-PRC + arousal + laterality + (1|PID) + (1|movie) + (1|movieRun);  $\chi^2(1) = 2.83$ ,  $\beta = -0.06$ , SE =

0.03,  $p = 0.09$ ; AIC tm: 492.80, AIC bm: 493.63; Figure 16). A fixed effect slope analysis of coupling of central-medial amygdala to perirhinal cortex interaction with arousal determined a significant slope of compression at high levels of arousal ( $\beta = -0.31$ , SE = 0.14,  $t = -2.23$ ,  $p = 0.03$ ; Figure 16), but not at low ( $p = 0.81$ ; Figure 16) or medium levels of arousal ( $p = 0.14$ ; Figure 16).

Basolateral amygdala to perirhinal cortex functional connectivity findings were not significant nor showed a trend towards significance for a main effect of functional coupling (Table 10). Further, the functional connectivity of the basolateral amygdala to the perirhinal cortex did not show an interaction with ROI coupling by arousal, ROI coupling by hemisphere, or ROI coupling by arousal by laterality 3-way interaction to predict distance estimation (Table 10).

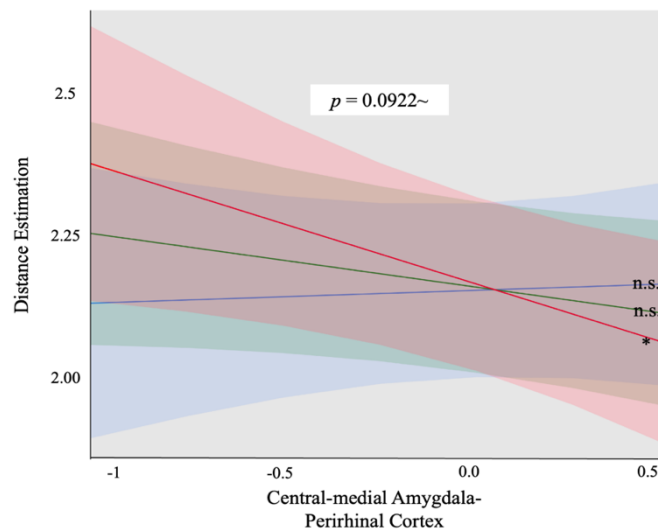


Figure 16: Functional Connectivity of Central-Medial Amygdala-Perirhinal Cortex in Distance Estimation.

Temporal distance was predicted by more in-sync central-medial amygdala-perirhinal cortex functional coupling during interaction with arousal (blue, low arousal; green, medium arousal; red, high arousal).

Table 10. Functional connectivity model comparisons of distance estimation (best-fit models in gray highlight/white text)

Basolateral amygdala to perirhinal cortex					
		$x^2$	$\beta$	<i>SE</i>	p-value
	BLA to PRC: non-interaction	1.8944	-0.1334	0.0967	0.1687
	BLA to PRC: interaction with arousal	0.2529	0.0188	0.0373	0.6150
	BLA to PRC: interaction with hemisphere	0.2124	0.0881	0.1911	0.6449
	BLA to PRC: interaction with arousal/hemisphere	0.0475	-0.0156	0.0713	0.8275
Central-medial amygdala to perirhinal cortex					
		$x^2$	$\beta$	<i>SE</i>	p-value
	CEM to PRC: non-interaction	2.0975	-0.1351	0.0932	0.1475
	CEM to PRC: interaction with arousal	2.8348	-0.0588	0.0348	0.0922
	CEM to PRC: interaction with hemisphere	0.0115	0.0200	0.1866	0.9146
	CEM to PRC: interaction with arousal/hemisphere	0.0893	-0.0206	0.0688	0.7651

## Study 2 Results Discussion

In all, Study 1 and Study 2 which examined retroactive estimation of elapsed time following threat-related arousal encoding have provided evidence of behavioral bias for immediate memory over delay, but neural findings confirm our brain-related arousal model of memory.

The presented neural findings have offered evidence to confirm our brain-related arousal model of memory (see Figure 17) but offer more complexity than we originally predicted. In sum, our univariate finding of the perirhinal cortex and our functional

connectivity finding between central-medial amygdala to anterior hippocampus 3-way interaction with arousal and hemispheric laterality at low levels of arousal indicate an expansion of distance estimation, which was not within our initial hypotheses. We did confirm our hypotheses of compression of distance estimation for our functional connectivity findings between basolateral amygdala to anterior hippocampus in interaction with low to medium arousal, basolateral amygdala to posterior hippocampus in a non-interaction model, central-medial amygdala to anterior hippocampus 3-way interaction with arousal and hemispheric laterality at high levels of arousal, and central-medial amygdala to perirhinal cortex interaction with high arousal.

In investigating how these findings were overall impacted by the temporal order of events, while we did not see our behavioral findings lasting to a 24-hour delay test, we believe the findings of distance estimation help to understand how the fMRI scanning environment may have impacted our models across Study 1 and Study 2. As participants seemed to be more attentive to both aversive and neutral clips in Study 2 compared with Study 1, we feel that including both an objective measure of temporal order memory and the subjective measure of distance, estimation was important for navigating our findings of threat-related arousal and temporal order memory. Importantly, we endeavored finally with this distinction between objective temporal order memory and subjective distance memory in both Study 1 and Study 2. These findings confirm our previous results, that arousal can bias memory via the amygdala, hippocampus, and cortical-MTL structures, but the wider conclusions about the full scope of these regions will be discussed in Chapter 5.

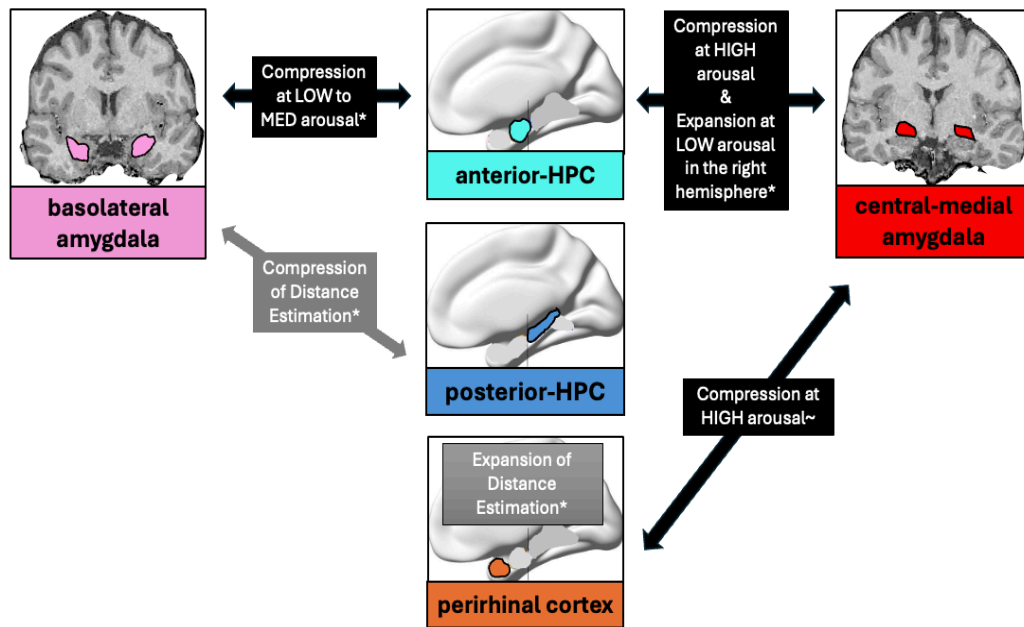


Figure 17: Summary of Distance Estimation Findings in Study 2. Univariate: PRC activity significantly predicts an expansion of distance estimation as activity increases, without interactions. Functional coupling: BLA to aHIP coupling significantly interacts with arousal, showing compression of distance estimation at low to medium arousal as coupling is more in-synch; BLA to pHIP coupling significantly predicts a compression of distance estimation as coupling is more in-synch, without interactions; CEM to aHIP coupling significantly interacts with arousal and laterality, showing expansion of distance estimation at low arousal as coupling is more in-synch and compression of distance estimation at high arousal as coupling is more in-synch; CEM to PRC shows a trend of coupling interacting with arousal, showing compression of distance estimation at high arousal as coupling is more in-synch. All models tested at significance of  $p < 0.05$ .

## **CHAPTER 5**

### **GENERAL DISCUSSION**

The adaptive facilities of animal memory to perceive danger and learn from aversive experiences are well observed, from rodents to dogs, to humans (J. E. LeDoux, 2000; Pavlov, 2010). Recently, advances have been made to study specific domains of threats with psychophysiological arousal during encoding and ensuing retrieval. The ability to do this seems to rely on both emotionally driven arousal and its influence on neural functional mechanisms at encoding (Clewett & Murty, 2019). Prior work shows that threat-related memory relies on relationships within the MTL, especially the amygdala, hippocampus, and perirhinal cortex (LaBar & Cabeza, 2006; Murty et al., 2010; Pape & Paré, 2010), but less work has explored these interactions in the domain of temporal memory (Cliver et al., 2024). Here, we considered and characterized the influence of threat-related arousal on temporal memory.

Behavioral and neural findings within the MTL have characterized the role of context, items, event boundaries, and motivation on temporal memory (Davachi, 2006; DuBrow & Davachi, 2014; Dunsmoor et al., 2022; Eichenbaum et al., 2007; Hsieh & Ranganath, 2014). Recently, behavioral work has shown that negative emotion enhances temporal memory (Dev et al., 2022; Petrucci et al., 2024; Petrucci & Palombo, 2021), but this work did not isolate the specific role of arousal as well as its underlying neural systems during encoding. The influence of arousal has been widely shown to be mediated by the amygdala, but with conflicting findings as to when and why amygdala engagement leads to memory improvements and impairments (Bennion et al., 2013; Cahill &

McGaugh, 1998; LaBar & Cabeza, 2006; Murty et al., 2011; Murty & Adcock, 2017; Tyng et al., 2017; Yonelinas & Ritchey, 2015).

These discrepancies in the role of arousal on memory may be due to (1) the type of memory being probed (item versus associative comparisons, or those with subjective versus objective comparisons), or (2) that many studies characterize the amygdala as a unified structure rather than identifying the separable roles between sub-nuclei, such as the basolateral and central-medial amygdala (Gregory et al., 2020). From these studies and additional background reviewed in Chapter 1, we predicted behaviorally that arousal would benefit temporal order memory performance and compression of distance estimation of retrospective elapsed time. Neurally, we predicted that interactions of the amygdala with MTL memory regions would predict temporal memory measures, but the basolateral amygdala and central-medial amygdala would show an encoding bias via modulatory relationships with MTL memory targets (hippocampus and perirhinal cortex). Specifically, we predicted that threat-related arousal would enhance temporal memory and that this would be driven predominately by the basolateral amygdala when arousal is low to moderate and by the central-medial amygdala when arousal is high. Given that temporal memory can be resolved either by item-based or associative strategies, we did not have strong predictions about targets across the hippocampus and perirhinal cortex.

Prior work in the domain of temporal memory mainly used static images, such as word lists or a series of pictures (Ezzyat & Davachi, 2014). In this dissertation, we opted to use a more naturalistic approach by characterizing the temporal memory of short video clips. The use of more naturalistic stimuli to better portray the real world has increased along with technological advances, to better study memory using movie clips

(Baldassano et al., 2017; Chen et al., 2017; Hasson et al., 2010; Swallow et al., 2009; Vanderwal et al., 2019), and virtual reality (Reggente et al., 2018; Scott et al., 2022), and following an in-person museum experience (Diamond & Levine, 2020). For our studies, using movie clips offered a balance between ecologically valid stimuli and scanning during encoding.

To test our hypotheses, we focused on our selected threat-related arousal in response to encoding movie clips and its downstream consequences on memory. Behaviorally, we considered both arousal and valence, and neurally we characterized ROI activity within a region (i.e., univariate), and functional connectivity across regions (i.e., amygdala connectivity with MTL memory regions). Broadly speaking, we found that the sub-nuclei of the amygdala, the central-medial amygdala, and the basolateral amygdala, engaged the anterior hippocampus, posterior hippocampus, and perirhinal cortex under varying states of arousal to predict temporal memory, but these relationships changed as a function of what type of memory was tested. For recency discrimination, we found univariate posterior hippocampus and functional coupling of central-medial amygdala to anterior hippocampus predicted better temporal order memory. For distance estimation, we found functional coupling of basolateral amygdala to anterior hippocampus, central-medial amygdala to anterior hippocampus, and central-medial amygdala to perirhinal cortex predicted compression of retrospective assessments of elapsed time, while univariate perirhinal cortex and, surprisingly, central-medial amygdala to anterior hippocampus predicted expansion. Importantly, for distance estimations different sub-regions of the amygdala showed different interactions with arousal in service of memory, with basolateral amygdala-anterior hippocampus

interactions predicted expansion during low to medium arousal, while central-medial amygdala to anterior hippocampus predicted compression during high arousal and expansion during low arousal, and central-medial amygdala to perirhinal predicted expansion during high arousal. We further found the central-medial amygdala to anterior hippocampus showed laterality effects, in both the left and right hemispheres for recency discrimination and distance estimation, respectively. As such, while we did not have support for our theoretical model in the domain of recency discrimination, we confirmed evidence for our model in the domain of distance estimation.

### **Threat-related Arousal of Temporal Order Memory**

Our behavioral findings helped to determine whether we should focus our subsequent neural analyses on arousal versus valence, as both are important in other domains of memory (Costanzi et al., 2019; Kensinger, 2004; Mather, 2009). Given the manipulation strategy at encoding, our selection of stimuli, and our overall theoretical foundation (Clewett & Murty, 2019; Murty & Adcock, 2017), a clear focus on arousal-related threats was supported by prior literature and our behavioral findings. In theory, we followed memory-related arousal research which has shown negative and aversive experiences impact memory of threats (Bradley et al., 1992; Cahill & McGaugh, 1998), but as described in Chapter 2, we specifically designed a study without positive stimuli and were interested in specific questions about threat detection and arousal.

In line with this theoretical work, behaviorally, at an immediate memory test, we found that arousal was a significant predictor of better temporal order memory queried via recency discrimination, while valence was not. Thus, we focused our neurobehavioral analyses in our imaging studies on the modulating role of arousal rather than valence.

Surprisingly we did not find a modulatory role for arousal on recency discrimination when memory was tested after a 24-hour delay in our fMRI study. We feel that this may be due to the scanning environment during fMRI increased baseline arousal levels, which impacted behavior. Another possibility is the delay of 24 hours as a source of differences between testing represents a degradation of the impact of arousal on behavioral temporal memory.

When considering how arousal might influence temporal order memory, there could be multiple behavioral mechanisms, which we could not arbitrate in the current study. One mechanism of sequential reactivation would require that individuals have both memory for the details of individual still images as well as a more gist-based memory of the entire narrative, so they can place those still images within the larger narrative and resolve temporal order. An alternative mechanism of relative familiarity would require individuals to recognize each of the still images and assess how “old” the stimuli feel in terms of the recollected memory (DuBrow & Davachi, 2017). While we are not able to unpack these mechanisms purely through behavior, we can garner insight into what strategies participants are using by leveraging the neuroimaging data. Specifically, if memory success is driven by amygdala-hippocampal interactions, this may suggest a more associative strategy of sequential reactivation, whereas if memory success is driven by amygdala-perirhinal cortex interactions, this may suggest an item-based strategy of relative familiarity (Clewett & Murty, 2019; Davachi, 2006; LaBar & Cabeza, 2006).

Following the literature and methodology, our neural findings of recency discrimination are less concrete in terms of arousal-related effects. We originally hypothesized arousal would impact temporal order memory with better performance, and

while we did see interactions with arousal, the threat-related neural circuitry involved the hippocampus and central-medial amygdala. This, again, could be because of delay or scanning environment, but we did see these variables predict better temporal memory. Specifically, we saw the posterior hippocampus in univariate activity increase with temporal order memory of recency discrimination. The posterior hippocampus captures detailed information related to experience in encoded episodic memory, which implies that regardless of arousal, this ROI helps to better retain specific information that is critical for temporal order memory (Moscovitch et al., 2016). We also found that the central-medial amygdala-anterior hippocampus also predicted better temporal memory with more in-sync functional connectivity. This relationship may help to better track spatial relationships, or gist-level details (Murty & Adcock, 2017), which may represent dual functions of tracking and bolstering temporal order memory. Arousal may influence temporal order memory, but we did not include important ROIs in our analyses (see *Limitations* below), and considering more regions along the LC-NE modulatory system would affect arousal impacts. Yet, we do not show disruption of temporal order memory with our threat-related circuitry, and with the immediate memory test, we may see stronger impacts of arousal.

While we were not able to conclude the effects of arousal on temporal order memory, these findings do provide evidence for what time mechanisms individuals were using to resolve temporal order, as the hippocampus was involved in all our findings. This further highlights an interesting role that outside of the domain of arousal, the central-medial amygdala-anterior hippocampus may predict memory in non-threat domains, but more research is needed to fully justify this possibility.

## **Threat-related Arousal of Temporal Distance Memory**

Using the system described above for temporal order, we followed the same theoretical approach to characterize temporal memory for elapsed distance estimation. We primarily followed work relating to how distance estimation of within-movie clip intervals may be impacted by associative and item-based strategies (Davachi, 2006), as opposed to research looking at distance as a function of the exact length of stimuli (Palombo et al., 2016), we measured distance with responses at a subjective level (i.e., relative versus absolute assessments). With this measure there is no correct answer for the distance estimation value selected (very close, close, far, very far), and as such has a subjectivity of response to test our brain-based arousal model.

Following this theoretical and methodological avenue, behaviorally, again at the immediate memory test, we found that arousal was a significant predictor of a compression of temporal distance memory queried via distance estimation, while valence was not. Thus, we again focused our subsequent neurobehavioral analyses in imaging studies on the modulating role of arousal rather than valence and did not find a modulatory role for arousal on recency discrimination when memory was tested after a 24-hour delay in our fMRI study. While many of the same reasons as detailed above may hold here, distance at delay may be influenced by factors unknown at this time.

The idea that arousal could lead to a compression of temporal distance estimations at first glance is rather surprising. In all, our behavioral findings do not support the expansion of distance estimation when assessing the full-time length of stimuli in common measurements of time (Droit-Volet, 2013; Droit-Volet & Meck, 2007; Lake et al., 2016; Safi et al., 2024). These studies in terms of behavior show attention and arousal

lead towards longer estimations, but the neural circuitry does not seem to be linked. Yet, in terms of contextual stability using a within-event measure of item distance, findings have also been shown to be biased towards compressed distance estimation (Ezzyat & Davachi, 2014), which may better model our study of within-clip distance. This line of thinking implies that threats may cause a surge in attention and perception, which in turn could lead to contextual stability, which would cause compression. An alternative explanation may be that with increased attention there will be more items and events remembered, which eventually push elapsed distance further apart in recollection. The number of specific events recollected, within an experience would then dictate estimation. More events that do not have a close focus or perception could lead to expansion, as prioritization is less driven, while events with strong attention or perceptual qualities could lessen prioritization of others, possibly lower arousal events, and end in compression. People prioritize the most salient features of threatening events over more mundane features, thus there may be less relevant content leading to compression. Within temporal memory, it would follow that items are prioritized over context.

When considering how arousal might influence temporal distance memory, again, multiple behavioral mechanisms help to better explain our measure. If individuals remember the sequential nature of the movie clips, with details of the images and the full narrative clip, the elapsed representation could be determined by events within the experience to guide memory. This allows the placement of stills again to be within the larger narrative, but there is still a need to resolve temporal distance. The alternative explanation offered previously by DuBrow and Davachi (2014) may hold truer with distance estimation, such that if the still images of the movie clip were ascribed “old” or

“new” at episodic recall, it may be more relevant to consider the time-lapse estimation.

We do not have behavioral data to unpack this further, but we will use neuroimaging data to gain comprehension as to how these strategies impacted participants in our studies. We followed the same mechanistic thinking as presented above, first that a strategy of associate sequential reactivation may follow amygdala-hippocampal interactions more, and second that a strategy of item-based relative familiarity may follow amygdala-perirhinal cortex interactions (Clewett & Murty, 2019; Davachi, 2006; LaBar & Cabeza, 2006).

Following the literature and methodology, our neural findings of distance estimation show evidence of both strategies on how participants may have resolved encoding, but together they add to findings of threat-related arousal. As mentioned, we predicted compression for within-movie clip estimations of elapsed distance ratings, which was also shown in our neural findings. We did find expansion as well, which was surprising but emphasizes future directions of study. Specifically, we have evidence of distance estimation interacting with arousal, which gives confirmation for our model and helps to better understand why looking at the amygdala as a unified area may show conflicting findings. For compression of distance estimation, within functional connectivity, we found: 1) basolateral amygdala-anterior hippocampus interacted with low to medium arousal, 2) basolateral amygdala-posterior hippocampus showed no interaction, 3) central-medial amygdala-anterior hippocampus interacted with high arousal, and 4) central-medial amygdala-perirhinal cortex interacted with high arousal. For the expansion of distance estimation, we found that univariate perirhinal cortex revealed no interaction and functional coupling of more in-sync central-medial amygdala-

anterior hippocampus interacted with low arousal. Unpacking the threat-related neural circuitry for our distance estimation findings may be explained by both strategies of episodic memory, as we see ROIs that imply both spatial-based encoding (anterior hippocampus) and item-based encoding (posterior hippocampus, perirhinal cortex). But, as the basolateral amygdala shows compression at low to medium arousal, but the central-medial amygdala shows expansion at low arousal when seed-ROIs are functionally connected with the anterior hippocampus, it may signify the nature of amygdala function due to the gating of information being sent from the lateral area of the basolateral amygdala to MTL-targets (Pape & Paré, 2010). The differential hypothesis may explain some of these results, but across Study 1 and Study 2, our data reveals the importance of the amygdala sub-nuclei in modulating threat-related arousal during encoding as a part of the HPA-axis, LC-NE, and specific MTL-memory areas. This suggests that the central-medial amygdala and basolateral amygdala not only play different functional roles in arousal, but also that this may help to better explain the controversy within related fields, in both threat-related temporal memory, and possibly, as discussed below, with PTSD. This may reflect a foundation of Pavlovian threat learning, but in dimensions of psychophysiological arousal as a basis for brain-based arousal bias memory, we offer evidence of how encoding aspects impact episodic memory recollection.

### **Connecting to the Threat, Arousal, and Temporal Memory Literature**

In all, we have presented evidence that threat-related arousal during encoding impacts subsequent temporal order memory recollection, both behaviorally at an immediate test and neurally after a delay. Within the related threat literature, the

amygdala has long been shown as a main mediator in threat-related responses (Dunsmoor et al., 2015; Klüver & Bucy, 1997), and that threat-related amygdala engagement facilitates item-memory (Murty & Adcock, 2017). However, most of the work does not disambiguate among amygdala sub-nuclei that have different functional properties. The findings from this study contribute to this literature by showing that the amygdala should not be viewed as a unified structure, and sub-nuclei of the amygdala should be considered, especially during encoding. In fact, across our measures, we see that the amygdala also shows hemisphere effects, although less is known about how this may impact related memory research (AbuHasan et al., 2019). In connection with the emotional temporal order literature, we see evidence of arousal more than valence, but it is clear that both domains are important and need to be considered when analyzing how valence may impact the encoding of threat-related arousal for aversive, neutral, and positive material (Kensinger & Corkin, 2004; Mather, 2007).

Our previous work shows that arousal influences behavior on temporal memory, such that high arousal increases performance (Cliver et al., 2024), and this work builds upon findings and offers evidence for a model of brain-based arousal (Clewett & Murty, 2019) which also relates our findings to that of larger models of emotional memory models developed in our lab (Murty & Adcock, 2017). Neural and behavioral encoding methodology can incorporate aspects of our behavioral and neural temporal memory findings to inform future models.

### **Connecting to the PTSD Memory Literature**

Threatening experiences that elicit high levels of arousal may lead to intrusive memories, and at extremes contribute to the development of PTSD. Threat-related

arousal of traumatic events is thought to lead to distortions in hippocampal function and produce an abundance of intrusive negative memories (Hayes et al., 2011). Although generally accepted, this theory has been disputed specifically regarding whether the presence of traumatic, intrusive memories is foundational to the development of PTSD. On one side, PTSD is described as a memory disorder, but it is unknown if these memories are strengthened or weakened (Brewin, 2016), while another side argues that memory is not a hallmark or symptom of PTSD, but instead, other mechanisms may underlie factors that exist as central to the maintenance of PTSD (Rubin et al., 2008) (Rubin, 2011, p. 20). These factors may be how traumatic memory is disentangled from the pathogenic event and impacts diagnosis, treatment, and research. Then, following our findings and in alignment with this critique, if threat-related arousal does bias the natural formation of memory cohesion, it may be due to high-arousal disruption of events during encoding (Rubin et al., 2016). Specifically, we have evidence that arousal influences explicit markers of memory during encoding, which may be incorporated into looking closely at trauma events and encoding.

This dissertation has been motivated in part towards understanding the foundations and symptomology of PTSD. Given the current state of PTSD research concerning memory, studying the role of threat-related arousal on memory encoding could characterize the brain areas that may be foundational in building a neurobehavioral model of PTSD-related memory disruptions. Prior work has shown that PTSD is associated with temporal memory, such that participants show major deficits with special, item, and temporal information (Layton & Krikorian, 2002), and is reliably shown in further episodic dysfunction (Brewin, 2014; Dere et al., 2010; Isaac et al., 2006; Moradi

et al., 2008). These disruptions in temporal memory may relate to how PTSD can result in intense flashbacks of clear episodic recollection, along with disorganized memory (Rubin, 2011). It is known that these types of memories can be highly vivid and last in long-term physiological responses, but if both items and special aspects are disrupted, these memories may be related to trauma or threat-related arousal. Understanding how item-based strategies and spatial strategies could be disentangled with encoding manipulations may be important to assess PTSD.

Further, our lab has shown evidence of PTSD-related impairments in hippocampal neurophysiology in threat-related dysfunction of the MTL. In Tanriverdi et al. (2022), we found that decreased hippocampal threat sensitivity interacts with a fear-potentiated startle to predict PTSD symptoms. Specifically, individuals with high fear-potentiated startle and low hippocampal threat sensitivity showed the greatest PTSD symptomology. Importantly, greater fear-potentiated startle determined a stronger relationship between decreased fear reactivity in the hippocampus and PTSD symptoms. This biased relationship along with our possible brain-based model of arousal, may show that temporal distance memory expands or compresses, both of which would be interesting. For temporal order memory, with less hippocampal tracking, PTSD symptoms may also show worse performance with sequential tracking, as witnessed during our studies. These findings bridge the works of literature on threat-related arousal and hippocampal function to better understand PTSD risk, however, the sequelae of the full model of the neural circuitry of threat-related arousal are unknown. It may be that PTSD is highly individualized, which would need to be understood in more subjective terms, yet there are indications that memory distortions of PTSD may relate to the

encoding of trauma events or experiences, which has been theorized within the literature (Bedard-Gilligan et al., 2017).

### **Limitations of These Studies**

The research presented within this dissertation partially confirmed our primary hypotheses of threat's influence on episodic memory for time. However, there are limitations to this study that must be considered. First, we did not find hypothesized effects of encoding arousal ratings predicting temporal order memory or temporal distance estimations when measured at delay in Study 2. As previously mentioned, the delay itself could explain this effect or the environmental difference during encoding across studies (online vs in-person fMRI). Yet, our fMRI findings support conclusions that arousal does indeed engage neural circuitry in service of temporal memory, at least for temporal estimation differences, in Study 2, suggesting that baseline differences in arousal due to the encoding environment may have led to negative findings at the group level.

Second, in the current study, we did not look at neural areas outside of the MTL or the influence of other neurochemical influences in our findings, especially medial prefrontal cortex, BNST, brainstem, and cerebellum ROIs. Many of these regions are directly connected to threat-related neural circuitry and are important for modulatory effects along the LC-NE pathway. Future studies with specific theoretical milieu could make use of both our data and stimuli to help better understand the neural and modulatory nature of the brain and body during threat-related arousal encoding.

Third, we did not fully consider valence and coherence variables in our analyses, which most likely would need to extend beyond our model of brain-based arousal to be

better understood within our findings. This would be important considering the interplay between arousal and valence, which needs more methodological approaches with naturalistic stimuli, and the ways coherence can be understood as a factor in concert with arousal and/or valence, or on its own. Coherence may be especially important when considering other neural circuitry systems beyond threat-related arousal.

### **Future Directions**

This dissertation lays down the tracks for understanding the neural basis of the granularity at which threat detection is influenced by arousal and how this relationship may bias subsequent temporal memory. But there remain open questions yet to be answered that are directly related to our current study, and others far afield from the current study.

The questions within the scope of our data are especially those of which we have unanalyzed measures, including assessments of arousal via heart rate (i.e., heart rate, heart rate variability), use of valence, coherence, reaction time, and individual differences with questionnaires, a larger whole-brain analysis to find important brain areas outside of the MTL. Additional analyses could also be performed on comparisons of conditional differences to non-conditional differences, the incorporation of reaction times during retrieval, and recency discrimination ratings. Incorporating these further studies may bolster our findings.

The answer to these questions of additional studies could also be helped with additional studies to measure threat-related arousal neural circuitry outside the MTL. As mentioned in Chapter 1, while the impact of directly connected regions and functionally connected regions to our ROIs was beyond our hypotheses, the importance of the

prefrontal cortex bed nucleus of the stria terminalis (BNST) is of high importance in arousal literature (Grinfeld & Likhtik, 2018; Lebow & Chen, 2016; Mashour et al., 2022). Research concerning brainstem arousal and the distance of threats have been widely shown (Gu et al., 2023) and would be a consideration with different approaches in stimuli and methodology. Also, the cerebellum is relevant in trauma-related research (Blithikioti et al., 2022) but is highly understudied within cognitive neuroscience (Popal, 2023).

Another aspect of our data is that our participants were scanned on Day 8, which will be further developed in considering reconsolidation factors in doctoral research for my research partner, Büşra Tanrıverdi. Significantly, we did not have data to determine how threat-related arousal neural circuitry during encoding impacts memory from immediate measure to delayed measure. While we have evidence for an immediate memory effect of arousal, we do not have the behavioral findings used in Study 2. Alternatively, performing a delay memory test following online procedures in Study 1 may help clarify the effects of in-person fMRI testing. Before these findings, we predicted that arousal effects would be the same from an immediate to a delayed memory test, but considering both our studies it may be that threat-detection arousal has a depreciating impact on memory over time, countering models of the amygdala's role in threat-driven memory consolidation. Finally, when considering the modulatory influence of the LC-NE system, the use of transcranial magnetic stimulation may help to improve findings beyond the use of one modality to study threat-related arousal related to the engagement of amygdala-cortical activation following stimulation (Sydnor et al., 2022).

## **Final Remarks**

In conclusion, our studies offer substantial data apropos to threat-related arousal at encoding engaging sub-nuclei of the amygdala, hippocampus, and perirhinal cortex, resulting in different temporal memory outcomes. Specifically, our results underscore the role of the sub-nuclei of the amygdala in biasing the MTL during encoding in the context of threat-related arousal, leading toward better temporal order memory performance and the balance between the compression and expansion of temporal distance estimations.

In brief, we found a significant univariate activity of the posterior hippocampus and perirhinal cortex predicted better temporal order memory and expanded temporal distance memory, respectively. Further, our functional connectivity results showed significant relationships between compressed temporal distance memory and interactions across the basolateral amygdala to the anterior hippocampus during low to medium arousal, basolateral and central-medial amygdala to the anterior hippocampus during high arousal, and central-medial amygdala to the perirhinal cortex during high arousal. Interestingly, we further found that temporal distance expansion was predicted by central-medial amygdala to anterior hippocampus interaction with low arousal. Taken together, disparate areas of research will help to develop our brain-based arousal model further (Clewett & Murty, 2019). There is support for our model in the context of temporal distance estimation, but also calls for new models on how threat-related arousal may influence the resolution of temporal order memory. Thus, the current dissertation surmises Darwin's insights, describing threats, arousal, and memory in support of real-world encoding as they exist along a spectrum from general attention to extreme terror (Abed & St John-Smith, 2024).

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