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Human medial temporal lobe theta oscillations underlying
visual exploration and approach-avoidance conflict in real-world spatial navigation

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy
in Neuroscience

by

Humza Nisar Zubair

2026

ABSTRACT OF THE DISSERTATION

Human medial temporal lobe theta oscillations underlying
visual exploration and approach-avoidance conflict in real-world spatial navigation

by

Humza Nisar Zubair

Doctor of Philosophy in Neuroscience

University of California, Los Angeles, 2026

Professor Nanthia Suthana, Co-Chair

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Theta oscillations in the medial temporal lobe (MTL) are linked to spatial navigation, memory, and active decision making, processes disrupted in disorders such as Alzheimer's. However, the role of MTL theta activity during naturalistic human behavior remains poorly understood. Much prior work in humans has relied on stationary laboratory tasks or surface EEG, paradigms that fail to capture the complexity of theta and real-world navigation. Describing MTL theta in freely-moving human behavior is therefore essential for relating intracranial electroencephalographic activity with the navigation and behavioral impairments observed in neuropsychiatric disorders.

Critical differences exist across species which obfuscate our comprehension of theta physiology. In rodents, hippocampal theta is expressed continuously during movement, while human theta occurs in transient bouts and is influenced by context and navigational challenges.

This dissertation explores how MTL theta activity is modulated by behavioral context during naturalistic navigation, with an emphasis on visual exploration, locomotive planning, and threat-reward evaluation.

Using intracranial recordings from human epilepsy patients with chronically-implanted neurostimulation (RNS®) implants, we demonstrate that theta activity in the hippocampus and amygdala is dynamically elevated during specific context-dependent periods of navigation. In Chapter 1, we demonstrate that MTL theta power is significantly elevated during periods when saccadic eye movements occur, particularly during periods with overt memory demands. The largest increases are observed during saccades with more exploratory gaze patterns, during saccades of trials with better memory performance, and during saccades in the early planning period of each route. In Chapter 2, we introduce a novel paradigm in which participants navigate under different levels of approach-avoidance conflict, while tracking goal locations and mobile threats. We demonstrate a double dissociation in which theta in the hippocampus increases during high-conflict contexts, and theta in the amygdala is elevated during high-risk contexts..

These findings collectively suggest that human MTL theta is a flexible and context-sensitive signal which supports prospective planning and decision-making during real-world navigation. We provide a framework for understanding oscillatory dynamics in freely moving humans, which will inform the development of effective context-dependent neuromodulation interventions for patients with diseases of the hippocampus and/or amygdala.

The dissertation of Humza Nisar Zubair is approved.

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2026

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SELECT CONFERENCE PRESENTATIONS

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Zubair HN, Martelo MV, Schneiders J, Gill J, Jang A, Mustapha R, Baham J, Koek RJ, Seeber M, Stangl M, Hiller S, Topalovic U, Inman C, Bari A, Kao J, Adhikari A, Fanselow M, Craske M, Krah S, Chen JWY, Vick M, Hasulak N, Suthana N, Langevin JP (2023) Responsive Neurostimulation for Post-Traumatic Stress Disorder: Interval Update. NINDS Therapeutic Development Project Meeting, Washington, D.C.

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Chapter 1

Eye Movements Reflect Memory-Related Theta Activity in the Human Brain

Abstract

Numerous studies across species emphasize the importance of theta oscillations within medial temporal lobe (MTL) regions, such as the hippocampus, in relation to memory. In rodents, physical movement strongly influences theta activity, while this relationship remains more ambiguous in primates. This disparity could stem from an increased reliance on visual search in primates. To explore this, we analyzed intracranial electroencephalographic (iEEG) activity from the human MTL recorded simultaneously with body and eye movements during ambulatory navigation. We found that MTL theta power was significantly higher during periods when saccadic eye movements were taking place, and this effect was observed only during periods with overt memory demands. The largest increases occurred during saccades with more variable and exploratory gaze patterns, on trials with better memory performance, and during the early planning period of each route. The modulation was also amplified near environmental boundaries, spatial features known to anchor memory representations and guide navigation. Together, these findings reveal that theta dynamics in the human MTL are tightly coupled to visual search and prospective planning during memory-guided navigation, revealing a mechanism by which saccades may help organize mnemonic computations in naturalistic settings.

1.1 Introduction

Theta oscillations (~5-8 Hz) within medial temporal lobe (MTL) regions, including the hippocampus, play a central role in episodic memory and spatial navigation across species (Guderian et al., 2009; Hoffman et al., 2013; Jutras et al., 2013; Maoz et al., 2023; Meister & Buffalo, 2016; Vivekananda et al., 2021). While theta activity in rodents is strongly modulated by physical movement, studies in humans have reported a stronger association with memory processes (Seger et al., 2023). This apparent discrepancy may arise from methodological differences: rodent studies typically involve recordings during free movement, whereas human studies often rely on stationary, view-based virtual navigation paradigms (Stangl et al., 2023). As a result, the contributions of memory and movement to theta dynamics in humans remain difficult to disentangle. Ideally, resolving this question requires recording neural activity from deep brain structures like the MTL during naturalistic, ambulatory behavior. Yet, such data remain rare due to the technical challenges of capturing intracranial signals while participants are actively moving.

Recent technological advancements have enabled mobile intracranial electroencephalographic (iEEG) recordings from the MTL in humans, enabling concurrent investigation of body movements (Topalovic et al., 2020). These techniques have confirmed the presence of movement-related hippocampal theta activity in humans (M. Aghajan et al., 2017). However, the manifestation of these oscillations varies across human and non-human primate studies (Herweg et al., 2020; Mao, 2022; Mao et al., 2021; Maoz et al., 2023). A potential explanation for this inconsistency could lie in the contrasting modes of exploration employed by primates and rodents. While rodents primarily rely on tactile exploration, particularly through their whiskers, human and non-human primates heavily depend on their well-developed visual system to navigate their surroundings (Grion et al., 2016; Mao, 2022; Nau et al., 2018). Understanding

how visual exploration shapes MTL theta is therefore essential for interpreting cross-species differences. Humans further offer the unique advantage of following rapidly shifting task instructions, allowing the effects of movement, visual exploration, and memory demand to be examined within a single experimental framework (Stangl et al., 2023).

In this study, we analyzed mobile iEEG recordings that were simultaneously captured with both body and eye movements as human participants engaged in a real-world ambulatory spatial navigation task. Through alternating task conditions, we systematically modified instructions to modulate ongoing memory demands. Our findings highlight a significant association between MTL theta activity and saccadic eye movements, but only when navigation relied on internal memory retrieval. The largest increases occurred during saccades with more variable and exploratory gaze patterns and on trials with better memory performance, as well as during the early planning period of each route, when participants generated internal predictions about potential target locations. These modulations were further amplified near environmental boundaries, spatial features that anchor memory representations. During memory-guided navigation, theta power also tended to rise during both locomotion and stationary periods, consistent with broad engagement during active information gathering. In addition, theta exhibited phase resetting to saccade onset during both memory-guided and visually guided navigation, indicating that eye movements may impose a consistent temporal structure on ongoing MTL activity regardless of memory demand.

Together, these results indicate that human MTL theta is tightly coupled to exploratory visual search and prospective planning during memory-guided navigation, providing a framework for reconciling variable findings across species and experimental paradigms.

1.2 Saccades Modulate MTL Theta Activity

We analyzed mobile iEEG recordings in five individuals who were surgically implanted with the RNS System (NeuroPace Inc., Mountain View, CA) in the MTL for the treatment of chronic epilepsy (Figure 1.1A-B) (Stangl et al., 2021; Topalovic et al., 2020). Alongside the iEEG signals, we examined eye and body movements captured while participants were engaged in a spatial navigation task within a rectangular room (Figure 1.1C, Supplementary Figure 1.1A). During the spatial navigation task, participants alternated between two conditions: 1) Visually-cued navigation, where participants walked toward one of 20 distinct wall-mounted signs and 2) Memory-cued navigation, where participants recalled and navigated to previously learned hidden target locations within the room (see 1.10 Methods).

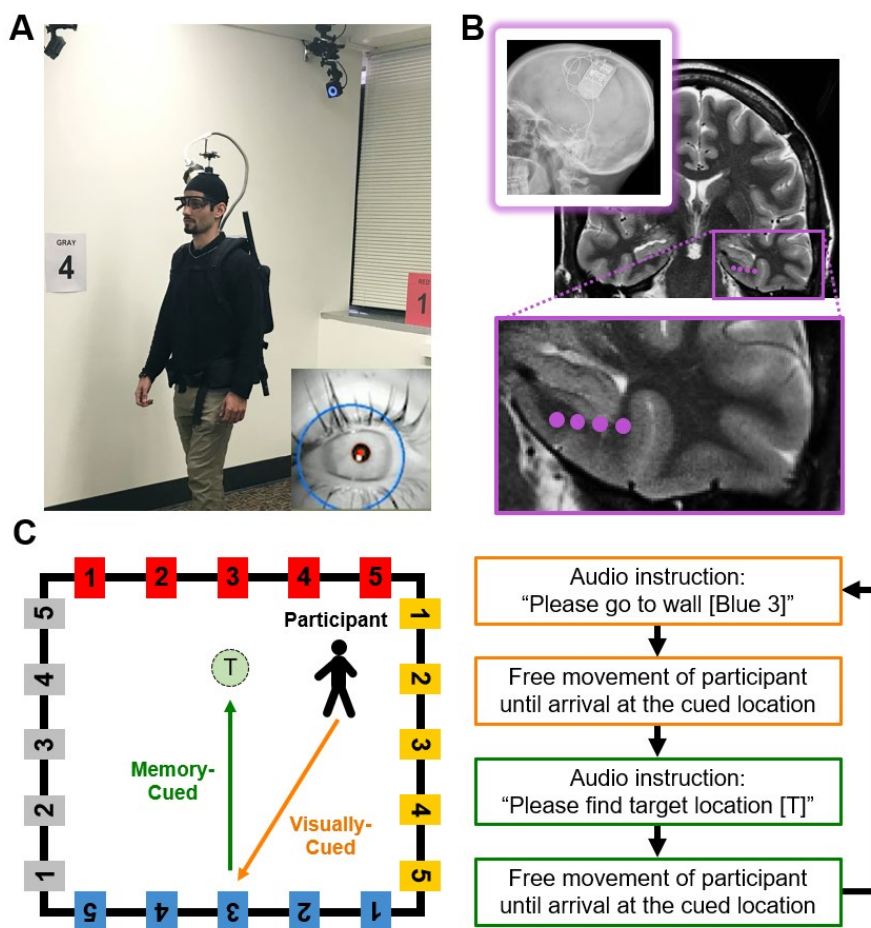


Figure 1.1. Experimental design and task. (A) Intracranial electroencephalographic activity, eye and body movements were recorded as participants freely walked around the room. Wall-mounted motion-tracking cameras recorded the position of on-body reflective markers. Participants also wore an eye-tracking headset to monitor saccadic eye movements. A snapshot from the eye-facing camera is shown in the bottom right. For illustrative purposes, an experimenter is shown wearing the full setup. (B) MRI of an example participant with an implanted RNS System. Purple dots indicate the location of four electrode contacts in the left medial temporal lobe (MTL). The top left inset shows an X-ray used to localize electrode positions. (C) The environment contained twenty visible wall-mounted signs and three invisible circular target locations (0.7 m diameter). At the start of the task, participants freely explored the room to locate the invisible targets; each time a target was reached, an auditory tone signaled success, allowing them to gradually learn and remember these locations through experience. The task then alternated between two conditions: “visually-cued” navigation, during which participants navigated to a wall-mounted sign (e.g., “Blue 3”), and “memory-cued” navigation, during which they recalled and navigated to the previously learned invisible targets (e.g., “T”).

To determine the impact of eye movements on MTL activity during ambulatory spatial navigation, we computed power across a wide frequency spectrum (2-80 Hz) at all recorded timepoints, comparing periods with saccadic eye movements to fixations (see 1.10 Methods). Channel-level statistics across the five participants were computed using the Permutation Analysis of Linear Models (PALM) framework (Winkler et al., 2014), which constrains permutations within participants. This approach maintains appropriate statistical independence while preventing effects from being driven by any single individual. Because PALM operates at the level of individual channels while preserving participant structure, we report channel-level analyses throughout the manuscript. Using this approach, we observed a significant increase in MTL power within the low-frequency range (~ 3 -15 Hz) during saccades compared to fixation periods when aggregating across channels ($N_{\text{channels}} = 16$; $t = 3.71$, $p < 0.001$; Figure 1.2A-B). Additionally, we found that low-frequency power rose gradually following saccade onset, with statistically significant increases

beginning 16 ms post-onset ($N_{\text{channels}} = 16$; $p < 0.05$; Figure 1.2C-D). Saccade duration varied substantially (median: 64 ms; interquartile range: 52 ms; $N_{\text{saccades}} = 29,747$), with most lasting less than 100 milliseconds (Supplementary Figure 1.1B).

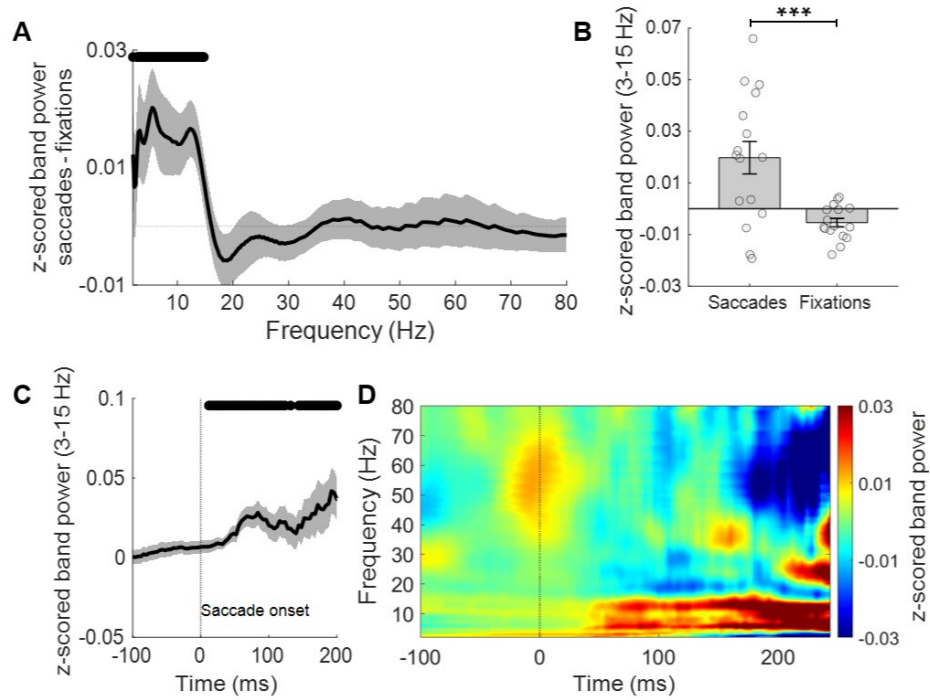


Figure 1.2. Saccadic eye movements are associated with increases in MTL low-frequency power. (A) Normalized (z-scored) band power differences between saccades and fixations across frequencies (2-80 Hz). Positive values indicate higher power during saccades. A significant increase was observed in the 2.75-14.75 Hz range (black horizontal bar = $p < 0.05$). (B) Mean low-frequency (3-15 Hz) power was significantly greater during saccades compared to fixations ($*** = p < 0.001$). Circles represent individual MTL channels ($N = 16$); error bars show $\pm$ SEM). (C) The increase in low-frequency power emerged gradually following saccade onset (dotted vertical line at time = 0) with statistically significant elevations following saccade onset (dotted vertical line, time = 0). Black horizontal bars = $p < 0.05$. (D) Heatmap showing normalized power over time and frequency, aligned to saccade onset (time = 0). A clear post-saccade increase was observed in the 3-15 Hz band. Warmer colors reflect higher power values. Normalization (z-scoring) was based on mean theta power across all fixation and saccade periods pooled across conditions, ensuring that contrasts were not biased by short pre-saccadic windows. Shaded gray regions in (A) and (C) represent $\pm$ SEM across channels ($N_{\text{channels}} = 16$).

1.3 Saccade-Related Theta Activity Depends on Memory

Given the established link between memory and MTL theta oscillations during spatial navigation (Buzsáki, 2002; Jutras et al., 2013; Rutishauser et al., 2010; Seger et al., 2023), we examined how task demands influenced saccade-related oscillatory activity. Memory-cued navigation required participants to encode and retrieve target locations, processes intrinsically linked to theta function (Buzsáki, 2002; Hasselmo et al., 2002), whereas visually-cued navigation relied on continuous visual access to the target, minimizing memory demands. As previously reported (Stangl et al., 2021), MTL low-frequency power was elevated during memory-cued compared to visually-cued navigation, particularly in the 2-3.75 Hz and 6.75-17.5 Hz ranges ($N_{\text{channels}} = 16$; $p < 0.05$; Supplementary Figure 1.4A). We next investigated whether this task-dependent difference in MTL oscillatory activity could be driven by eye movements, given their central role in visual processing. As summarized in Supplementary Table 1.1, participants completed the same number of trials across conditions, and the number of saccades and fixations were also identical. Interestingly, saccade-related increases in MTL theta power were significantly more pronounced during memory-cued than visually-cued navigation, specifically within the 5.75-7.5 Hz range (Supplementary Figure 1.4B). As a result, our subsequent analyses focused on the 5-8 Hz frequency range. Indeed, we observed that this MTL theta band power exhibited an increase during memory-cued navigation, primarily during saccades, in contrast to fixation periods ($N_{\text{channels}} = 16$; $t = 2.37$, $p = 0.012$; Figure 1.3A). This increase unfolded gradually after saccade onset, reaching statistical significance after 48 ms ($p < 0.05$; Figure 1.3B-C). In contrast, no significant theta modulation by saccades was observed during visually-cued navigation ($N_{\text{channels}} = 16$; $t = 0.31$, $p = 0.376$; Figure 1.3D-F). Direct comparison between conditions confirmed that saccade-related power was significantly greater during memory-cued versus visually-cued navigation

($N_{\text{channels}} = 16$; $t = 2.16$, $p = 0.019$; Figure 1.3G). Supplementary Video 1.1 illustrates trial-level data from a representative participant, showing enhanced theta activity during saccades in memory-cued but not visually-cued navigation.

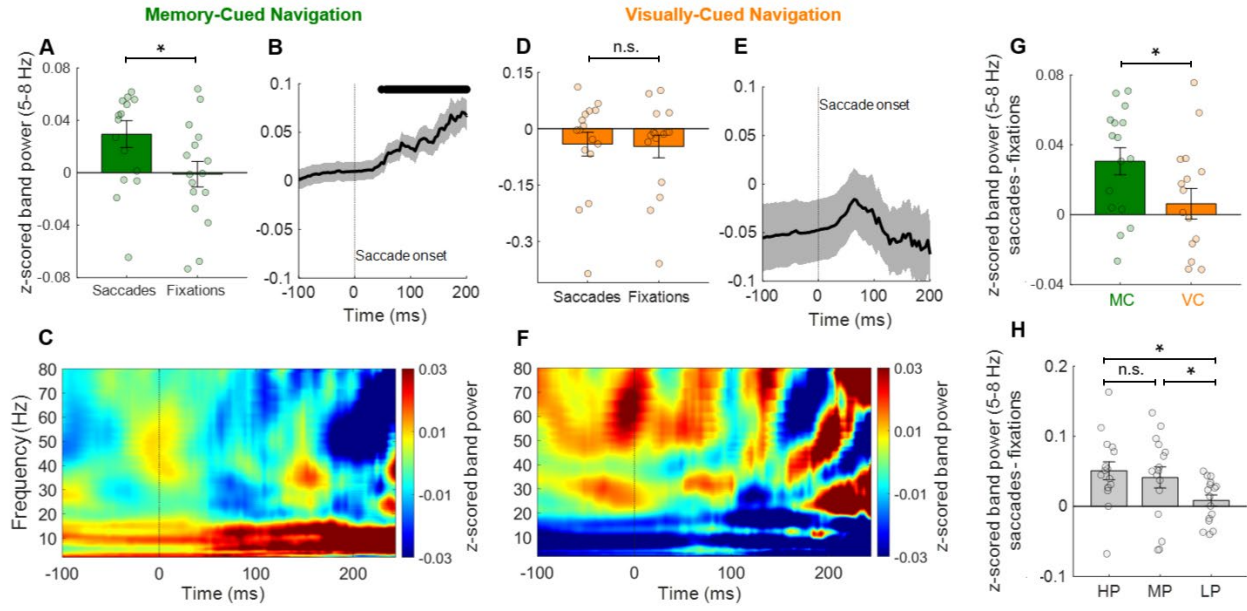


Figure 1.3. Saccade-related theta activity depends on memory demands. (A) During memory-cued (MC) navigation, MTL theta (5-8 Hz) power was significantly higher during saccades compared to fixations ($p = 0.012$). (B) Theta power gradually increased after saccade onset (time = 0), with significant elevations beginning at 48 ms (black bars = $p < 0.05$). (C) Heatmap shows sustained low-frequency power increases following saccade onset (time = 0). (D) During visually-cued (VC) navigation, MTL theta (5-8 Hz) power did not significantly differ between saccades and fixations ($p = 0.376$). (E) No significant theta increases were observed after saccade onset (time = 0). (F) Heatmap shows no saccade-related increases in low-frequency power, but peaks in gamma (45-80 Hz) power appeared around saccade onset (time = 0). (G) Saccade-related theta power (saccades – fixation difference) was significantly greater during MC vs. VC navigation ($p = 0.019$). (H) Theta power increases were stronger during high-performance (HP) and medium-performance (MP) MC trials compared to low-performance (LP) trials. Panels A, D, G, and H show mean ($\pm$ SEM) across 16 MTL channels (circles). For B and E, shaded gray = standard error of the mean (SEM) across channels ($N_{\text{channels}} = 16$). Warmer colors in C and F reflect higher power values. * = $p < 0.05$, n.s. = not significant.

To determine whether differences in saccadic modulation of theta power could be explained by variations in eye movement behavior across conditions, we compared key oculomotor metrics between memory-cued and visually-cued navigation (Supplementary Figure 1.1D). Specifically, we examined saccade frequency, duration, displacement, and fixation duration. No significant differences were found between the two task conditions in any of these measures ($N_{\text{participants}} = 5$; saccade frequency: memory-cued = 2.4 ± 0.2 Hz, visually-cued = 2.3 ± 0.2 Hz, $t = 1.12$, $p = 0.15$; saccade duration: memory-cued = 89.0 ± 3.7 ms, visually-cued = 88.8 ± 3.6 ms, $t = 0.47$, $p = 0.47$; saccade displacement: $t = -0.53$, $p = 0.31$; fixation duration: 342.1 ± 30.8 ms vs. 370.8 ± 32.1 ms, $t = -1.20$, $p = 0.18$). These results indicate that the observed saccade-related theta modulation cannot be attributed to differences in eye movement behavior across task conditions.

1.4 Saccades, Not Body Movement, Predict Memory-Related Theta Activity

Prior studies have shown that MTL theta power can be influenced by variables such as proximity to environmental boundaries (Maoz et al., 2023; Stangl et al., 2021) and walking speed (M. Aghajan et al., 2017). To disentangle the effects of eye and body movement, we applied linear mixed-effects models separately for memory- and visually-cued navigation. In the memory-cued condition, eye movement speed significantly predicted theta power ($N_{\text{participants}} = 5$; $t = 3.15$, $p = 0.032$), whereas body movement speed did not ($N_{\text{participants}} = 5$; $t = -0.97$, $p = 0.818$; Supplementary Figure 1.4C). In contrast, during visually-cued navigation, neither eye nor body movement speed significantly modulated theta power ($N_{\text{participants}} = 5$; $t = 0.10$, $p = 0.436$ and $t = -0.31$, $p = 0.656$, respectively).

We next examined whether saccade-related theta increases were modulated by other behavioral contexts. We quantified z-scored theta power during saccades across four contexts: near boundaries, in inner regions, at higher locomotion speeds (movement), and while stationary

(Supplementary Figure 1.5A-H). Saccade-related theta increases were significant only near boundaries during memory-cued navigation ($N_{\text{channels}} = 16$, MC: $t = 2.62$, $p = 0.006$; VC: $t = -0.02$, $p = 0.506$; MC vs. VC: $t = 2.51$, $p = 0.008$; Supplementary Figure 1.5A-B). In contrast, no significant effects were observed in inner regions for either condition ($N_{\text{channels}} = 16$, MC: $t = 1.00$, $p = 0.163$; VC: $t = 0.66$, $p = 0.163$; MC vs. VC: $t = 0.45$, $p = 0.324$; Supplementary Figure 1.5C-D). During movement and stationary periods, effects trended towards significance only during memory-cued navigation (movement: MC: $t = 1.60$, $p = 0.060$; VC: $t = 0.10$, $p = 0.462$; MC vs. VC: $t = 1.70$, $p = 0.051$; Supplementary Figure 1.5E-F; stationary: MC: $t = 1.35$, $p = 0.095$; VC: $t = 0.14$, $p = 0.440$; MC vs. VC: $t = 1.62$, $p = 0.058$; Supplementary Figure 1.5G-H). Taken together, these results show that the observed increases are not explained by locomotion or general movement state and instead appear most robust near boundaries, where spatial information is especially salient for memory-guided navigation.

1.5 Saccade-Related Theta is Strongest During Early Phases and Successful Memory

Given that saccadic modulation of MTL theta power was observed only during memory-cued navigation, we investigated whether this effect varied with memory performance. Behavioral performance was quantified by the walking detour distance (error) on each memory-cued navigation trial (see 1.10 Methods). Saccade-related MTL theta power was significantly higher in high-performance (HP) and medium-performance (MP) trials compared to low-performance (LP) trials ($N_{\text{channels}} = 16$, HP vs. LP: $t = 2.40$, $p = 0.027$, MP vs. LP: $t = 2.09$, $p = 0.032$, HP vs. MP: $t = 0.34$, $p = 0.373$, FDR corrected, Figure 1.3H). Furthermore, the difference in theta power between saccades and fixations reached significance only in HP and MP trials ($N_{\text{channels}} = 16$, HP: $t = 3.68$, $p = 0.001$; MP: $t = 3.26$, $p = 0.003$), but not in LP trials ($N_{\text{channels}} = 16$, $t = 1.34$, $p = 0.095$). Importantly, these theta power differences were not driven by changes in eye movement behavior,

as saccade duration, frequency, displacement, and fixation duration showed no significant differences across performance groups (all $p > 0.1$; Supplementary Figure 1.1E). Together, these findings indicate that memory-related MTL theta activity in humans is closely linked to saccadic eye movements, with this relationship being strongest when memory performance is successful.

To further examine the temporal dynamics of theta activity within memory-guided navigation, we divided each memory-cued trial into an early (“planning”) and late (“execution”) half. The first half corresponded to initial route planning and search behavior, while the second half reflected execution of the recalled path toward the hidden target. Theta power during saccades was significantly higher than during fixations in the first half ($N_{\text{channels}} = 16$, $t = 2.29$, $p = 0.013$; Supplementary Figure 1.2A), but not in the second half ($N_{\text{channels}} = 16$, $t = 0.68$, $p = 0.254$; Supplementary Figure 1.2B). The difference in saccade–fixation theta modulation between halves was significant ($N_{\text{channels}} = 16$, $t = 1.79$, $p = 0.041$; Supplementary Figure 1.2C). In contrast, visually-cued navigation showed no significant saccade–fixation modulation in either half: first half ($N_{\text{channels}} = 16$, $t = -0.120$, $p = 0.546$; Supplementary Figure 1.2D), second half ($N_{\text{channels}} = 16$, $t = 0.459$, $p = 0.327$; Supplementary Figure 1.2E), or their difference ($N_{\text{channels}} = 16$, $t = -0.761$, $p = 0.772$; Supplementary Figure 1.2F). We also confirmed that movement speed increased from planning to execution, consistent with behavioral expectations. Velocity was significantly higher in the second half than the first half for both memory-cued navigation ($N_{\text{participants}} = 5$, $t = -8.400$, $p = 0.030$; Supplementary Figure 1.2G) and visually-cued navigation ($N_{\text{participants}} = 5$, $t = -13.513$, $p = 0.031$; Supplementary Figure 1.2H), indicating that this temporal modulation of theta is not explained by changes in movement alone. Together, these findings show that saccade-related MTL theta activity is strongest during the early, planning-dominant portion of memory-guided trials and during successful retrieval, supporting a role for theta in anticipatory visual search and memory-

driven planning rather than low-level motor execution.

To assess whether observed saccade-related theta effects could be explained by systematic covariation among behavioral predictors, we directly examined relationships between trial phase, spatial context, performance, and eye movement metrics during memory-cued navigation. As expected from task structure, memory-cued trials typically began near the boundary, immediately following visually-cued navigation. Accordingly, participants spent a greater proportion of time near the boundary during the first compared to the second half of memory-cued trials ($N_{\text{channels}} = 16$; $t = 3.91$, $p = 0.032$). Saccade duration was also modestly longer during the first versus second half ($N_{\text{channels}} = 16$; $t = 2.92$, $p = 0.032$). These results indicate that early trial phase and boundary proximity are partially coupled in this task. Importantly, no other behavioral measures differed across these contrasts. Eye speed, scanpath entropy, and boundary occupancy did not differ across performance levels (all $p > 0.19$). Eye speed and scanpath entropy also did not differ between early and late trial phases (all $p > 0.25$), and saccade frequency, saccade displacement, and fixation duration were comparable between the first and second halves of memory-cued navigation (all $p > 0.15$). When comparing boundary and inner regions of the room, eye speed and scanpath entropy did not differ (all $p > 0.09$). Together, these analyses indicate that while early trial phase and boundary proximity co-occur due to task structure, the broader pattern of saccade-related theta modulation cannot be explained by a single behavioral confound or shared covariance among eye movement parameters, consistent with a role for internally driven planning processes that are most prominent early in memory-guided navigation.

1.6 MTL Theta Reflects Exploratory Eye Movements During Memory-Guided Navigation

We next examined how medial temporal lobe (MTL) theta activity relates to the magnitude, frequency, and spatial complexity of saccadic eye movements. Larger or more exploratory saccades may reflect greater shifts in visual sampling or planning effort during memory retrieval.

Saccade Magnitude

Saccades were categorized by magnitude using a median split, based on the two-dimensional displacement from saccade onset and termination. MTL theta power was significantly higher during large versus small saccades ($N_{\text{channels}} = 16$, $t = 3.28$, $p = 0.002$; Figure 1.4A). When analyzed by condition, this effect was present only during memory-cued navigation ($N_{\text{channels}} = 16$, $t = 2.72$, $p = 0.004$) and absent during visually-cued navigation ($N_{\text{channels}} = 16$, $t = 0.85$, $p = 0.204$; Figure 1.4B). The magnitude-related increase in theta power was also significantly greater in memory-cued than visually-cued navigation ($N_{\text{channels}} = 16$, $t = 2.20$, $p = 0.020$; Figure 1.4C). Across performance levels, theta power during large saccades was numerically higher in high-performance (HP) than in medium (MP) or low-performance (LP) trials, though differences did not survive FDR correction ($N_{\text{channels}} = 16$, *HP vs. MP*: $t = 2.29$, $p = 0.047$; *HP vs. LP*: $t = 1.69$, $p = 0.071$; *MP vs. LP*: $t = -1.02$, $p = 0.845$; FDR corrected; Figure 1.4D). These results indicate that saccade displacement magnitude modulates theta power specifically during memory retrieval, consistent with enhanced neural engagement during larger exploratory gaze shifts.

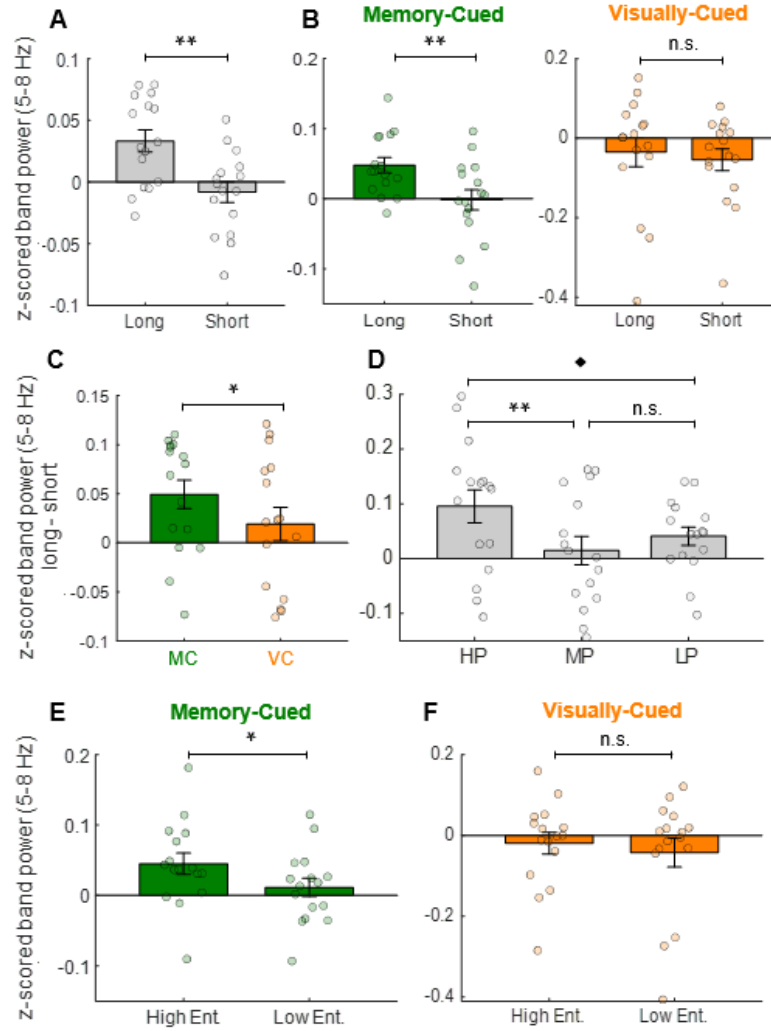


Figure 1.4. MTL theta activity scales with saccade magnitude during memory-guided navigation. (A) MTL theta (5-8 Hz) power was significantly higher during large compared to small saccades ($p = 0.002$). (B) This effect was present during memory-cued (MC) navigation ($p = 0.004$) but not during visually-cued (VC) navigation ($p = 0.204$). (C) The magnitude-related increase in theta power (difference between large and small saccades) was significantly greater during MC than VC navigation ($p = 0.020$). (D) During MC trials, saccade magnitude-related theta increases were stronger in high-performance (HP) trials than in medium (MP) and low-performance (LP) trials. (E-F) Mean normalized (z-scored) 5–8 Hz theta power during high- and low-entropy periods for each condition. Theta power was significantly higher during high-entropy periods in MC navigation ($p = 0.023$; E) and was not significant in VC navigation ($p = 0.158$; F). Panels A-F show mean ($\pm$ SEM) across 16 MTL channels (circles). $\blacklozenge = p < 0.1$, $* = p < 0.05$, $** = p < 0.01$, n.s. = not significant.

Saccade Frequency

We next assessed whether theta power varied by saccade frequency. One-second epochs were median-split by saccade count within each participant and condition. During memory-cued navigation, MTL theta power was trending higher during high- versus low-saccade periods ($N_{\text{channels}} = 16$, $t = 1.33$, $p = 0.096$; Supplementary Figure 1.4D – Left), while no significant difference emerged during visually-cued navigation ($N_{\text{channels}} = 16$, $t = -0.34$, $p = 0.630$; Supplementary Figure 1.4D – Right). The difference between high and low frequency epochs was greater for memory-cued than visually-cued navigation ($N_{\text{channels}} = 16$, $t = 1.72$, $p = 0.049$; Supplementary Figure 1.4E). These results suggest that theta power increases with the rate of saccadic sampling, particularly when visual exploration must rely on memory.

Scanpath Entropy

To quantify the spatial complexity of eye movements, we computed scanpath entropy using a grid-binned spatial occupancy approach (Harris et al., 1986; Melnyk et al., 2024). The visual field was divided into 30×30 bins, and Shannon entropy was calculated within 1-second sliding windows. For each participant, we then performed a median split of entropy values into high- and low-entropy time points and compared the corresponding 5–8 Hz z-scored theta power. In memory-cued navigation, theta power was significantly higher during high-entropy than low-entropy periods ($N_{\text{channels}} = 16$, $t = 2.06$, $p = 0.023$; Figure 1.4E), whereas in visually-cued navigation the difference was not significant ($N_{\text{channels}} = 16$, $t = 1.03$, $p = 0.158$; Figure 1.4F). These results suggests that greater gaze dispersion or more exploratory scanpaths are associated with stronger theta activity, particularly during memory-guided navigation. Together, these results indicate that MTL theta power may track multiple aspects of visual exploration, including saccade magnitude, frequency, and spatial dispersion, during memory-guided navigation. Theta thus

appears to reflect internal cognitive processes linked to active search and spatial planning rather than simple oculomotor behavior.

1.7 Saccades Induce Theta Phase Resetting Independent of Memory and Trial Phase

To test whether saccades elicit phase resetting of medial temporal lobe (MTL) theta, we computed pairwise phase consistency (PPC) across saccades (Vinck et al., 2010). Consistent with prior studies in humans and non-human primates demonstrating saccade-locked theta phase resetting (Hoffman et al., 2013; Jutras et al., 2013; Katz et al., 2020, 2022), PPC was significantly elevated around saccade onset from -60 to $+196$ ms relative to saccade onset ($N_{\text{channels}} = 16$, black bar = $p < 0.05$; Supplementary Figure 1.3A). Using a predefined saccade-onset window (-50 to $+200$ ms) and a baseline period of equal duration (-800 to -550 ms) (Hoffman et al., 2013), we confirmed that PPC during saccades was significantly higher than baseline across all navigation conditions ($N_{\text{channels}} = 16$, $t = 2.62$, $p = 0.002$; Supplementary Figure 1.3B), indicating reliable theta phase resetting associated with saccadic events.

When analyzed separately by task condition, phase resetting occurred in both memory-cued and visually-cued navigation. In memory-cued trials, PPC increased from -72 to $+208$ ms ($N_{\text{channels}} = 16$, black bar = $p < 0.05$; Supplementary Figure 1.3C) and was significantly higher during saccades than baseline ($N_{\text{channels}} = 16$, $t = 2.12$, $p = 0.006$; Supplementary Figure 1.3D). In visually-cued trials, a shorter window of significant PPC was observed from $+40$ to $+52$ ms ($N_{\text{channels}} = 16$, black bar = $p < 0.05$; Supplementary Figure 1.3E) and PPC during saccades was also significantly higher than baseline ($N_{\text{channels}} = 16$, $t = 2.70$, $p = 0.005$; Supplementary Figure 1.3F). The presence of phase resetting in both memory-cued and visually-cued navigation suggests that saccade-linked theta synchronization is not exclusively memory-dependent but may instead reflect a general mechanism coupling visual sampling with MTL timing. The longer post-saccade

duration in the memory-cued condition may point to sustained mnemonic or planning-related processes extending beyond immediate sensory updating.

To assess whether phase resetting varied across trial phases, we divided each trial into early (“planning”) and late (“execution”) halves. Theta phase resetting was significant in both early ($N_{\text{channels}} = 16$, $t = 2.51$, $p = 0.005$) and late ($N_{\text{channels}} = 16$, $t = 2.31$, $p = 0.004$) halves (Supplementary Figure 1.3G-J), suggesting that this synchronization accompanies saccadic events throughout navigation. Together, these findings suggest that saccades serve as temporal anchors for theta phase resetting in the human MTL, supporting both visual exploration and higher-order cognitive operations such as planning and memory retrieval.

1.8 Robustness of Results across Time-Frequency Parameters

Time-frequency analyses of electrophysiological data involves a trade-off between temporal and spectral resolution. Because saccades are extremely brief (typically < 100 ms), while theta oscillations are slower (5-8 Hz, corresponding to cycles lasting ~ 125 -200 ms), we aimed to maximize resolution in the time domain for our theta analysis. In our main analyses, we used a six cycle wavelet approach to balance this trade-off (Whitten et al., 2011). To ensure our findings were not dependent on this choice, we repeated the key analyses using a lower number of cycles (3), which improves temporal resolution at the cost of spectral precision. These control analyses confirmed our main results. Specifically, MTL low-frequency power (3-15 Hz) was significantly elevated during saccades compared to fixations ($N_{\text{channels}} = 16$, $t = 3.30$, $p = 0.001$; Supplementary Figure 1.6A). This increase remained specific to memory-cued navigation ($N_{\text{channels}} = 16$, $t = 2.28$, $p = 0.013$) and was not observed during visually-cued navigation ($N_{\text{channels}} = 16$, $t = 0.65$, $p = 0.258$; Supplementary Figure 1.6B). Within memory-cued navigation, saccade-related MTL theta band

power was again higher in HP and MP trials compared to LP trials ($N_{\text{channels}} = 16$, *HP vs. LP*: $t = 2.35$, $p = 0.012$; *MP vs. LP*: $t = 1.87$, $p = 0.035$; *HP vs. MP*: $t = 0.35$, $p = 0.365$; FDR corrected; Supplementary Figure 1.6C). Additionally, the saccade-fixation theta difference was significant only for HP and MP trials ($N_{\text{channels}} = 16$, *HP*: $t = 3.47$, $p < 0.001$; *MP*: $t = 2.75$, $p = 0.004$; *LP*: $t = 1.23$, $p = 0.112$).

When comparing high- versus low-entropy periods in MC navigation, theta power was elevated during memory-cued navigation ($N_{\text{channels}} = 16$, $t = 2.06$, $p = 0.023$) but not visually-cued navigation ($N_{\text{channels}} = 16$, $t = 1.03$, $p = 0.158$; Supplementary Figure 1.6D). Similarly, theta power was elevated during long versus short saccades exclusively in memory-cued navigation ($N_{\text{channels}} = 16$, $t = 2.71$, $p = 0.004$) but not visually-cued navigation ($N_{\text{channels}} = 16$, $t = 0.84$, $p = 0.205$; Supplementary Figure 1.6E). Comparing high- with low-frequency saccade periods revealed a trending increase in memory-cued navigation ($N_{\text{channels}} = 16$, $t = 1.33$, $p = 0.096$) and no increase during visually-cued navigation ($N_{\text{channels}} = 16$, $t = -0.34$, $p = 0.630$; Supplementary Figure 1.6F).

Moreover, we confirmed that in boundary regions, MTL theta power was elevated during saccades compared to fixations during memory-cued navigation ($N_{\text{channels}} = 16$, $t = 2.60$, $p = 0.007$) but not during VC navigation ($N_{\text{channels}} = 16$, $t = -0.02$, $p = 0.506$; Supplementary Figure 1.6G). For inner regions of the room, theta power did not differ between saccades and fixations for either memory-cued ($N_{\text{channels}} = 16$, $t = 1.16$, $p = 0.130$) or visually-cued navigation ($N_{\text{channels}} = 16$, $t = 1.01$, $p = 0.164$; Supplementary Figure 1.6H). Finally, comparing theta power between saccades and fixations revealed elevations during the first half of MC trials ($N_{\text{channels}} = 16$, $t = 2.29$, $p = 0.013$) but not during the second half ($N_{\text{channels}} = 16$, $t = 0.69$, $p = 0.251$; Supplementary Figure

1.6I). Overall, these results demonstrate that the observed saccade-related modulation of MTL theta during memory-guided navigation is robust across time-frequency parameters choices.

1.9 Discussion

Our findings demonstrate that during real-world ambulatory navigation, human medial temporal lobe (MTL) theta activity is shaped by memory demands and modulated by saccadic eye movements. We observed increased theta power during saccades, but only during successful memory-cued navigation, when target locations had to be internally recalled. This modulation was absent during visually guided navigation, where the target remained visible and no memory retrieval was required. Importantly, this saccade–theta relationship persisted regardless of the participant’s locomotion state, suggesting that eye movements, rather than physical movement, were the primary behavioral correlate of memory-related theta in this context.

A rich literature shows that the relationship between movement and theta differs markedly across species. In rodents, hippocampal theta oscillations in the 5 to 8 Hz range occur continuously during exploration and are strongly tied to movement speed (Bland, 1986; Vanderwolf, 1969). In contrast, humans, non-human primates, and bats exhibit theta in transient bouts, and its occurrence is less tightly coupled to movement (Courellis et al., 2019; Kahana et al., 1999; M. Aghajan et al., 2017; Mao et al., 2021; Stangl et al., 2021; Ulanovsky & Moss, 2007; Watrous et al., 2013; Yartsev et al., 2011). These species differences challenge canonical models that view theta as a movement-driven rhythm supporting memory and navigation (Giocomo & Moser, 2011). A likely explanation lies in differing sensory strategies. Rodents rely heavily on olfaction and whisking (Grion et al., 2016; Uchida & Mainen, 2003), whereas humans depend more on vision. In humans, theta may become more aligned with visual sampling through saccades, particularly when memory is

engaged. Consistent with this view, rodent studies show theta synchronizing with whisking during memory-guided object discrimination (Grion et al., 2016). Our results parallel this pattern, showing that in humans, theta becomes dissociated from movement and instead tracks saccadic eye movements during memory-guided navigation.

Prior work has linked MTL theta to successful memory. Theta power increases during spatial memory retrieval, precedes successful verbal encoding, and is elevated during visual exploration in monkeys when memory is later successful (Guderian et al., 2009; Jutras et al., 2013; Maoz et al., 2023; Vivekananda et al., 2021). Here, we extend these findings by showing that saccade-related MTL theta power is enhanced during memory-cued compared to visually-cued navigation and is most prominent during higher performance trials. Saccade-related theta amplitude scaled with saccade magnitude, but only in memory-relevant contexts, suggesting that saccades may help structure internal representations by enhancing interregional communication and integrating visual input with stored memories (Buzsáki, 2002; Hasselmo et al., 2002; Hoffman et al., 2013; Mao, 2022; Meister & Buffalo, 2016; Wagner et al., 2022). This mechanism may support prediction and goal-directed navigation.

We also found evidence of theta phase resetting around saccade onset, consistent with prior work in both humans and non-human primates (Hoffman et al., 2013; Jutras et al., 2013; Katz et al., 2020, 2022). Phase resetting was observed in both memory-cued and visually-cued navigation, suggesting that saccade-locked theta serves as a general temporal coordination mechanism in the MTL. However, the phase resetting persisted longer after saccade onset during memory-cued navigation, potentially reflecting additional mnemonic or planning-related processes. This observation supports models proposing that theta phase alignment provides a temporal framework for organizing perception and memory (Hasselmo et al., 2002; Lisman & Buzsaki, 2008).

It is important to note that peri-saccadic low-frequency power increases may partially reflect overlapping event-related potential (ERP) components, as reported in prior work (Katz et al., 2020, 2022). Such evoked responses can produce broadband low-frequency power that temporally coincides with theta activity. Nonetheless, our analyses emphasized time–frequency power averaged across many saccades and fixations, rather than single-trial ERP waveforms, and the presence of clear phase resetting (PPC) effects supports the interpretation that rhythmic synchronization contributes meaningfully to the observed signal.

Theta activity was not uniform across the course of a trial. Saccade-related theta power increases were stronger during the early, planning-dominant phase of memory-cued navigation than during later execution. Moreover, periods of higher scanpath entropy, reflecting more exploratory and dispersed gaze behavior, were associated with greater theta power. The link between exploratory viewing and theta echoes prior work showing that hippocampal theta in both humans and monkeys increases during active visual search (Jutras et al., 2013; Kaplan et al., 2012). This pattern suggests that theta may help organize internal predictions or spatial hypotheses before movement, supporting a transition from memory recall to forward-looking planning. In this view, hippocampal theta could act as a bridge between retrieving past experiences and simulating future trajectories, linking perception, attention, and memory into a cohesive planning process.

Previously, we showed that MTL theta is modulated by spatial location, movement speed, and behavioral demands (M. Aghajan et al., 2017; Maoz et al., 2023; Stangl et al., 2021). In those studies, walking speed was associated with theta increases only when memory was not explicitly engaged. Aghajan et al. (M. Aghajan et al., 2017) reported that theta prevalence increased with movement speed during a simple walking task without memory demands, and Stangl et al. (Stangl et al., 2021) found significant modulation of low-frequency power by speed during visually-guided

(“no target search”) but not memory-cued (“target search”) navigation. Using the same dataset as Stangl et al. (Stangl et al., 2021), the present study focuses on eye movement–related theta dynamics and similarly finds that movement speed did not significantly explain variance in theta power, whereas eye movements did (Supplementary Figure 1.4C). This pattern is consistent with our more recent memory-guided studies (Maoz et al., 2023; Seeber et al., 2025), which also found no relationship between theta and speed under mnemonic conditions. Together, these findings indicate that theta–speed coupling is characteristic of non-mnemonic or visually-guided locomotion, whereas during memory-guided navigation, theta dynamics reflect internal cognitive processes such as retrieval and planning rather than external movement parameters.

In related work, we found that theta increases prior to memory-guided turns, critical moments of route recall, were also associated with behaviorally relevant saccades (Seeber et al., 2025). Although eye movements explained significant variability in theta during walking, spatial position near moments of recall was a stronger modulator, likely because visual search demands were minimal. In the current task, however, participants used eye movements to search for hidden targets, emphasizing visual exploration during goal-directed search rather than route recall. Given prior evidence of stronger MTL theta near environmental boundaries [16], we also tested whether boundary proximity contributed to the observed effects. Here, saccade-related theta enhancements were significantly greater near boundaries but not within inner regions of the environment. This pattern suggests that boundaries amplify theta engagement during memory-guided exploration, potentially by anchoring spatial predictions or enhancing the retrieval of boundary-referenced representations. Together, these findings suggest that MTL theta flexibly couples to eye movements in memory-guided contexts, particularly when visual search supports the integration of sensory input with internal spatial representations.

Saccades are rapid, coordinated eye movements that play a central role in guiding attention and organizing perception (Souto & Kerzel, 2021). They are influenced by both bottom-up visual salience and top-down task goals (Doucet et al., 2020; Kragel et al., 2020; Niu et al., 2012; Voss et al., 2011; Zimmermann et al., 2014). Each saccade interrupts visual input and prompts the realignment of spatial reference frames, integrating egocentric and allocentric representations (Aagten-Murphy & Bays, 2019; Andrillon et al., 2015; Doucet et al., 2020; Mao et al., 2021), a process that is cognitively demanding. This momentary disruption may create brief windows of opportunity for memory-related neural computations (Crivelli-Decker et al., 2023; Doucet et al., 2020; Jutras et al., 2013). Despite their brevity, typically lasting less than 100 milliseconds, saccades appear to engage neural systems operating at slower timescales, such as theta oscillations, which cycle approximately every 125 to 200 milliseconds. This temporal mismatch suggests that saccade-related increases in theta may not be tied to individual saccades per se, but instead to broader cognitive states or sequences of saccadic activity.

Several possible mechanisms could explain the observed relationship between saccadic eye movements and theta activity. Theta may be elevated during bursts or clusters of saccades, as individuals scan the environment during memory retrieval. Alternatively, theta may reflect a cognitive state associated with saccade planning, such as attentional engagement or retrieval initiation, rather than the saccadic movements themselves. It is also possible that theta is suppressed during sustained fixations, with saccades marking moments of re-engagement or attentional reset. Another possibility is that saccades act as cognitive boundaries, triggering transient theta bursts that help segment experience and organize information in memory. Together, these possibilities support a view in which saccades serve not only as perceptual and motor events but also as functionally meaningful anchors for memory-related activity in the MTL.

The hippocampus and broader MTL are well-positioned to support this integration. Corollary discharge signals from oculomotor control regions provide information about saccade direction and amplitude to MTL circuits (Katz et al., 2022; Mao, 2022; Meister & Buffalo, 2016). This supports anticipatory visual coding and aligns with our finding that larger saccades induce greater internal map transformations (Staudigl et al., 2022; Wagner et al., 2022). Consistent with this, we found that saccade magnitude is associated with increased theta amplitude during memory retrieval. In contrast, this relationship was absent during visually guided navigation, where external cues reduce reliance on internal maps. Importantly, eye movement metrics were matched across task conditions, suggesting that theta differences reflect cognitive demands rather than low-level visual or motor differences. Thus, MTL theta appears to integrate visual exploration with internal memory representations only when memory is required to guide behavior.

In summary, our findings show that eye movements modulate MTL theta oscillations during naturalistic navigation, particularly in memory-guided contexts. These results underscore the central role of vision in structuring memory processes in humans and reveal that saccades may provide temporal scaffolding for theta-mediated memory computations. Given that visual exploration and spatial memory are altered early in Alzheimer's disease and related disorders (Coughlan et al., 2018; Dragan et al., 2017; Gert et al., 2022; Mehak et al., 2022; Ryan et al., 2007; Uhlhaas & Singer, 2006), saccade-linked theta may serve as a neural marker of memory function and a promising target for future interventions in both health and disease.

1.10 Methods

Participants

Five individuals (ages 31–52; three male, two female) with pharmacoresistant focal epilepsy participated in this study. All participants had indwelling depth electrodes implanted in medial temporal lobe (MTL) regions for clinical purposes. Electrode placement was determined solely based on clinical criteria. All participants volunteered for the study and provided written informed consent in accordance with a protocol approved by the UCLA Medical Institutional Review Board (IRB #17-001452), and this study was conducted in accordance with the ethical principles for medical research involving human subjects as outlined in the Declaration of Helsinki. Data reported here were collected as part of a previously published study (Stangl et al., 2021) and are reanalyzed to address novel hypotheses.

Behavioral Task

Participants performed a memory-guided spatial navigation task while freely moving within a rectangular room (approximately 5.9×5.2 m; $\sim 19.4 \times 17.1$ ft). Twenty wall-mounted signs displaying color-number pairs served as navigational cues, and three predefined circular target locations (0.7 m diameter) were invisibly positioned within the space (Figure 1.1C). Trials alternated between two types: (1) visually-cued navigation, where participants walked to a visible wall sign (e.g., “yellow 4”); and (2) memory-cued navigation, where they searched for a previously learned but currently hidden target location (e.g., “T”). Hidden targets were not shown prior to the task. Instead, during initial trials, participants were instructed to explore until they reached the correct location, at which point an audio tone signaled that they were within the target’s 0.7 m radius. This auditory feedback was repeated each time the target was reached, strengthening memory across trials. Each participant completed multiple blocks of alternating trial types (2–4

blocks, ~15 min each). The same hidden targets were repeated within a block (four for Participant 1; three for Participants 2–5), and the order of targets varied across blocks. During memory-cued trials, participants could either search freely or walk directly to the hidden target if recalled.

Performance on memory-cued trials was quantified using detour error, defined as the percent increase in walking distance relative to the optimal straight-line path. Trials were divided into low-, medium-, and high-performance trials by splitting the data into equal-sized thirds based on detour error scores. Participant 1 completed a slightly modified version of the task that included four hidden target locations. Additional observation-only task data from the original study were excluded from the present analysis. Full task details are described in Stangl et al. (Stangl et al., 2021).

Experimental Control and Data Synchronization

Real-time experimental control was implemented using a custom Unity application (version 2018.1.9f2). Participant position and heading were continuously tracked via a motion capture system, and behavioral events (e.g., arrival at a target) triggered auditory instructions and task progression. The application automatically detected key events, such as reaching a wall sign or hidden target, and issued the next instruction accordingly. Synchronization signals were sent to the implanted iEEG acquisition system at the start and end of each 3.5–4 minute recording segment to enable precise alignment with eye tracking and motion capture data. Technical details of the synchronization framework are provided in Topalovic et al. (Topalovic et al., 2020).

Eye Tracking and Saccade Detection

Mobile eye-tracking data were recorded using the Pupil Core headset (Pupil Labs GmbH) at ~200 Hz, with a spatial accuracy of 0.6°. Gaze position was calculated within a normalized 192 × 192 pixel reference frame. Data acquisition was performed using the Pupil Capture (v1.11) and

processed with Pupil Player (v1.11). Eye movements were classified as saccades or fixations using the Cluster Fix toolbox for MATLAB (König & Buffalo, 2014), which applies k-means clustering to velocity, acceleration, and displacement metrics. Clusters with the lowest combined velocity and acceleration were labeled as fixations, along with any within three standard deviations of that cluster's mean. All remaining clusters were classified as saccades. Each timepoint was labeled accordingly and used throughout all analyses to distinguish neural activity during saccades versus fixations (Supplementary Figure 1.1A). The distribution of saccade durations is shown in Supplementary Figure 1.1B.

Motion Tracking

Participant location was continuously tracked throughout the experiment using the OptiTrack system (Natural Point Inc., Corvallis, OR) and the MOTIVE software (version 2.2.0). Twenty-two wall-mounted infrared cameras captured the position of a rigid body marker, composed of multiple reflective markers affixed to the participant's head, at a sampling rate of 120 Hz with sub-millimeter precision. An additional camera from the system recorded a wide-angle video of the room for contextual reference during the experiment.

iEEG Data Acquisition

iEEG was recorded using the US Food and Drug Administration (FDA)-approved RNS System (Neuropace, Inc., Mountain View, CA), which is typically used for seizure detection and responsive stimulation. To eliminate stimulation artifacts during the experiment, therapeutic stimulation was temporarily disabled with the participant's informed consent, and the system was used solely for recording. Each participant had two implanted depth leads, each with four electrode contacts spaced either 3.5 mm or 10 mm apart. This configuration enabled continuous bipolar iEEG recording from up to four channels per participant, sampling at 250 Hz. iEEG data were

transmitted in real time via near-field telemetry using a Wand positioned over the implanted neurostimulator (Figure 1.1A). The Wand was mounted on a custom backpack worn by the participant, allowing free movement during recording (see Topalovic et al. (Topalovic et al., 2020) for technical details). Data were stored automatically in ~3.5-4 minute segments, with brief (~10 s) breaks between recordings. During these breaks, participants were instructed via computerized audio prompts to remain still.

Electrode Localization

High-resolution post-operative head computed tomography (CT) scans was acquired for all participants. Electrode contact locations were determined by co-registering each participants CT to their preoperative high-resolution structural magnetic resonance image (T1- and/or T2-weighted), as shown in Figure 1.1B. Recording contacts were localized to MTL regions, including the hippocampus, subiculum, entorhinal cortex, parahippocampal cortex and perirhinal cortex (Supplementary Table 1.2). No contacts were located in the amygdala. Channels outside the MTL were excluded from further analyses.

Detection of Epileptic Events

Epileptic events, including interictal epileptiform discharges (IEDs), were detected separately for each recording channel using a previously established method (Gelinas et al., 2016), which we have applied in prior RNS System studies (Aghajan et al., 2019; M. Aghajan et al., 2017; Stangl et al., 2021). The algorithm employs a double-thresholding approach based on two criteria (1) the envelope of the unfiltered signal exceeding six standard deviations above baseline, or (2) the envelope of the rectified signal filtered between 15–80 Hz exceeding the same threshold. To capture residual epileptic activity surrounding these events, the binary IED vector (1 for IED, 0 otherwise) was smoothed using a Gaussian filter with a 0.05 s window. All samples with smoothed

values above 0.01 were also marked as IEDs. This step effectively excluded a ~250 ms window around each detected IED. Using this method, an average of 1–2% of data per participant was identified as IED-related (range: 1.1% for participant 2 to 2.0% for participant 1), consistent with previous findings (M. Aghajan et al., 2017).

Participants were intentionally selected for relatively low IED activity. Using the RNS System's event log, we estimated each participant's average daily event count over the preceding three months and recruited those with fewer events (approximately 500–800 per day). All participants gave informed consent to disable stimulation during the experiment to eliminate stimulation-related artifacts in the iEEG recordings.

iEEG Data Analysis

Time–frequency analyses of iEEG data were conducted using the BOSC toolbox (Seager et al., 2002; Whitten et al., 2011), which includes both continuous wavelet-based power estimation and detection of oscillatory bouts based on duration and power criteria. For all main analyses, oscillatory power was computed using a continuous Morlet wavelet transform (implemented within the BOSC framework), which estimates time-resolved power at each frequency. Morlet wavelets of order six were applied across frequencies from 2 to 30 Hz in 0.25 Hz steps, and 31 to 80 Hz in 1 Hz steps. To quantify the prevalence of theta bouts, we additionally used the BOSC detection algorithm, which identifies time points where power exceeds the 95th percentile of a fitted background ($1/f$) distribution for at least two cycles; these results are reported in Supplementary Figure 1.1C.

BOSC and wavelet analyses were applied to each 3.5–4 minute recording interval on a sample-by-sample basis, providing high temporal resolution for linking transient neural dynamics to momentary behaviors such as saccadic eye movements. To ensure robustness, analyses were

repeated with a lower cycle (3) wavelet approach, reducing frequency resolution while improving temporal precision. Results remained consistent, indicating that our findings were not dependent on this trade-off (Supplementary Figure 1.6).

Following wavelet decomposition, band power was calculated by averaging across defined frequency bands (e.g., 5–8 Hz for theta). Power time series were normalized by z-scoring each frequency band within each recording interval and channel. These normalized time series were aligned with eye-tracking labels (saccade or fixation), and average power was computed for samples of interest (e.g., all saccade-labeled samples).

To examine relationships between behavior and theta dynamics, we used linear mixed-effects models with normalized theta power as the response variable. Eye movement speed and body movement speed served as fixed-effect predictors, while recording channels were included as random effects to account for variability across channels and participants. Importantly, eye movements were modeled as a continuous variable (magnitude per time point), rather than as categorical saccade/fixation labels. All predictor variables were standardized prior to model fitting, allowing direct comparison of effect sizes. Standardized beta weights indicate the relative contribution of each predictor. Models were fitted separately for memory-cued and visually-cued navigation conditions (Supplementary Figure 1.4C).

To further assess the relationship between MTL theta activity and saccade frequency or entropy, we segmented the continuous iEEG data into overlapping one-second windows with a 4 ms step size. For each window, we calculated the average theta power and the total number of saccades. Windows were then categorized into high- and low-saccade-frequency groups (or high- and low-saccade-entropy groups) based on a median split of the saccade count (or entropy) distribution within each participant and condition. Average theta power was computed separately

for high- and low-frequency saccade windows within the memory-cued and visually-cued navigation conditions. This windowed analysis allowed us to examine how ongoing fluctuations in saccade frequency related to theta dynamics during different task conditions.

Data Subsampling for Statistical Analysis

Because participants freely walked around the environment during the experimental task, it is possible that they spent more time in one task condition (e.g., memory-cued vs. visually-cued navigation, or vice versa) which would affect statistical comparisons (for example, comparisons of band power) between these conditions. Similarly, statistical comparisons between saccades and fixation periods could be biased by differences in their prevalence or duration throughout the task. To ensure balanced comparisons, we performed all analyses on 500 iteratively generated, equally sized subsets of data. For each participant, we first determined the number of samples in each condition, then subsampled from the condition with more data to match the smaller condition. Parameters of interest (e.g., wavelet-based power estimates) were computed on each matched subset. This procedure was repeated 500 times, and results were averaged across iterations. This approach was applied consistently across both eye movement and navigation condition comparisons. All reported statistics and plots are based on these equal-sized, averaged datasets.

Statistical Testing

For participant-level analyses (e.g., Supplementary Figure 1.1D), statistical comparisons were performed using one-sided permutation tests with 10,000 permutations, as all hypotheses were directional (e.g., expecting higher theta power during saccades vs. fixations, or during memory-cued vs. visually-cued navigation). For paired data, condition labels were shuffled, and the mean difference was recalculated repeatedly to build a null distribution. The observed mean difference was then tested against this distribution. To assess whether a single set of values (e.g.,

mean power) differed from zero, we randomly flipped the sign of each value, recalculated the mean, and repeated this 10,000 times to create a null distribution. The true mean was then compared to this distribution. In all permutation-based tests, p-values were computed by counting permutations with values greater than or equal to the observed statistic (i.e., including ties). This approach provides an accurate estimate of the probability of observing the test statistic under the null hypothesis and prevents underestimation of p-values. All channel-level analyses were implemented using the PALM framework [17], which constrains permutation exchangeability within each participant, allowing valid inference without assuming independence across electrodes. Multiple comparisons were corrected using the false discovery rate (FDR) method where applicable (e.g., Figures 1.3H and 1.4D) [60].

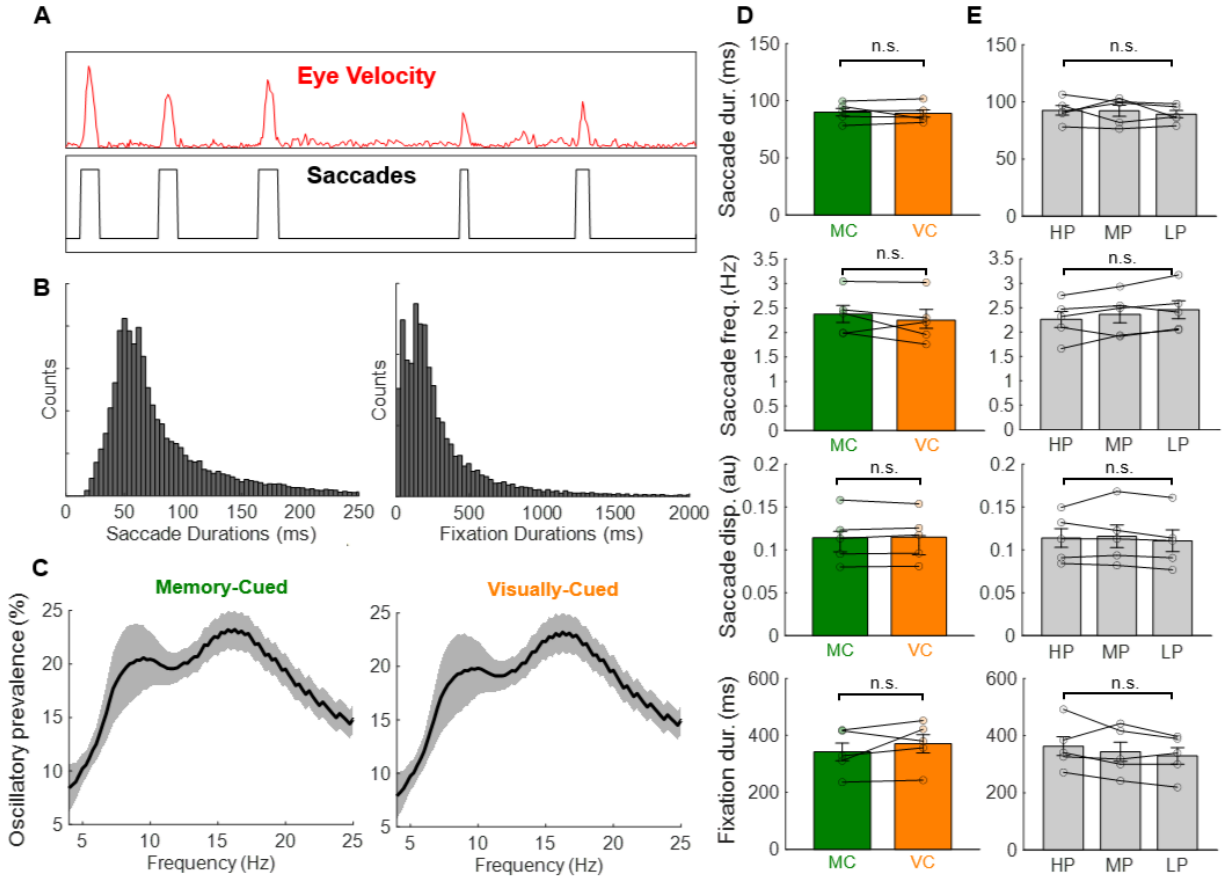
Temporal Analysis

To examine the timing of neural activity around saccade onset, we extracted oscillatory power from 100 ms before to 200 ms after each saccade. For normalization, baseline power was defined as the mean theta power across all fixation and saccade periods pooled across both task conditions. To isolate activity specific to the transition from fixation to saccade, we excluded pre-saccade data points (−100 to 0 ms) that overlapped with prior saccades, and post-saccade points (0 to +200 ms) that overlapped with subsequent fixations. As a result, the temporal plots (line graphs, heat maps) reflect the transition from fixation (−100 to 0 ms) to saccade onset and progression (0 to +200 ms). Because saccade durations varied across events (Supplementary Figure 1.1B), timepoints further from saccade onset are more likely to overlap with fixations and were excluded, reducing the number of saccades contributing data at later timepoints. At each timepoint, we averaged oscillatory power across all qualifying saccades, separately for each recording channel.

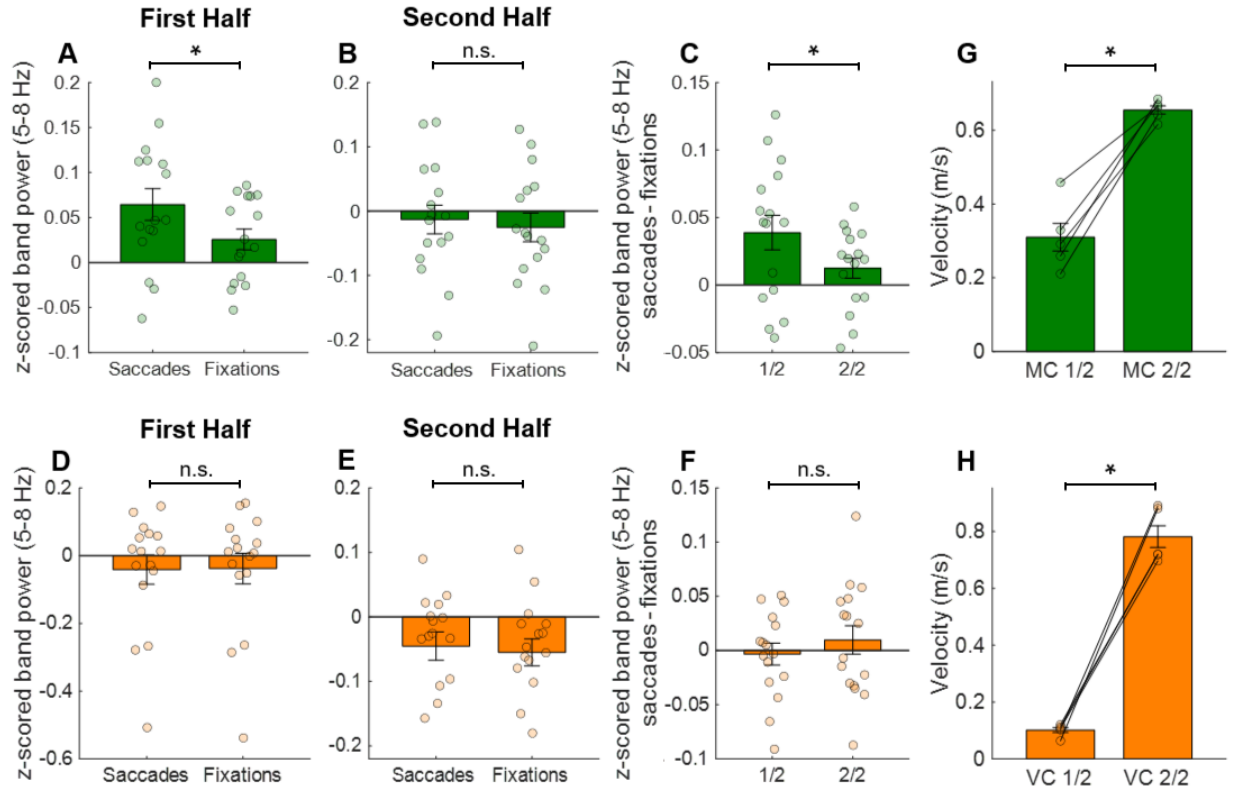
For heatmaps (e.g., Figures 1.2D, 1.3C, 1.3F), we visualized oscillatory power across time (4 ms steps) and frequency (2–30 Hz in 0.25 Hz steps, 31–80 Hz in 1 Hz steps).

Data and Code Availability

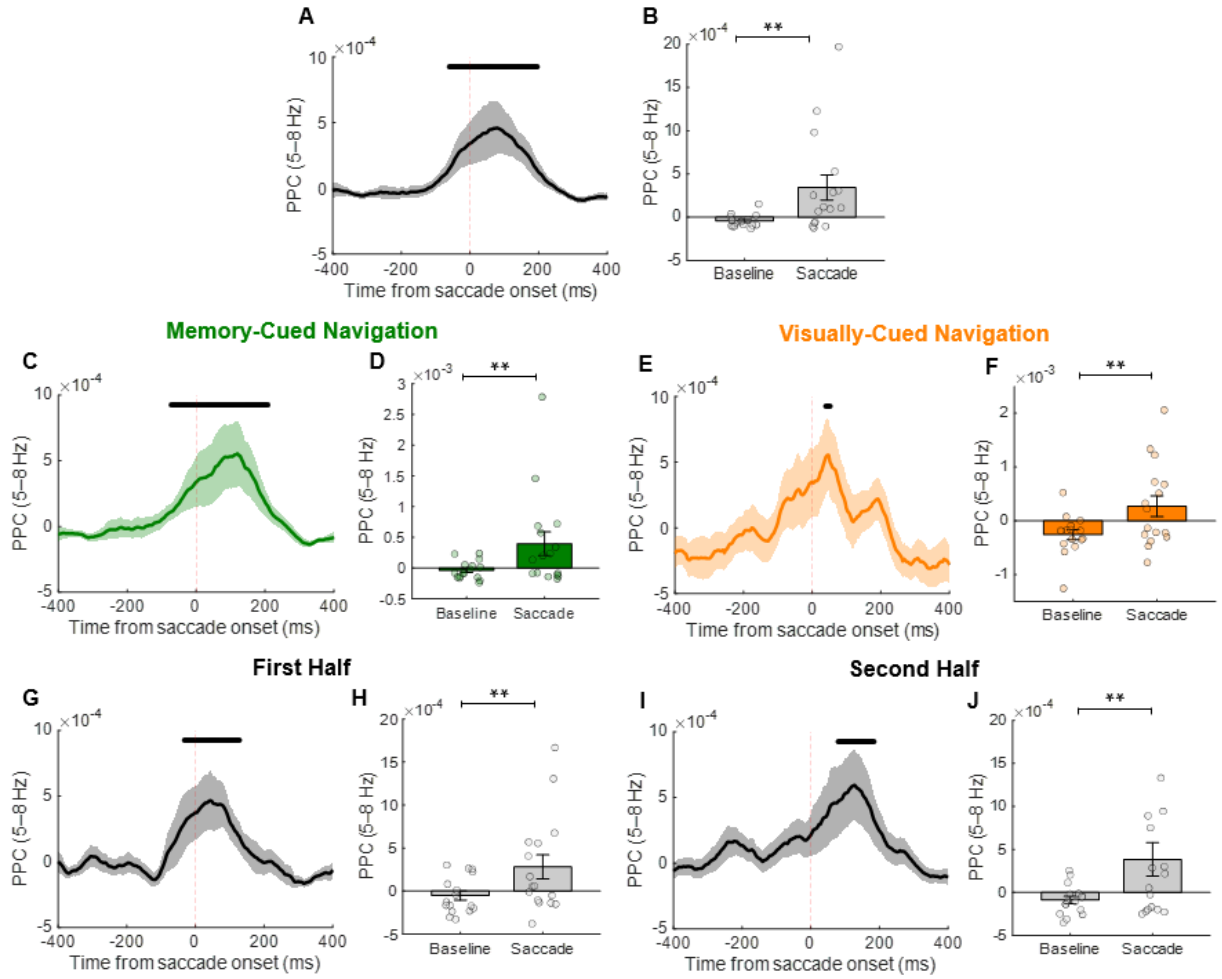
The data supporting the findings of this study are openly available via Zenodo at <https://doi.org/10.5281/zenodo.18487389>.



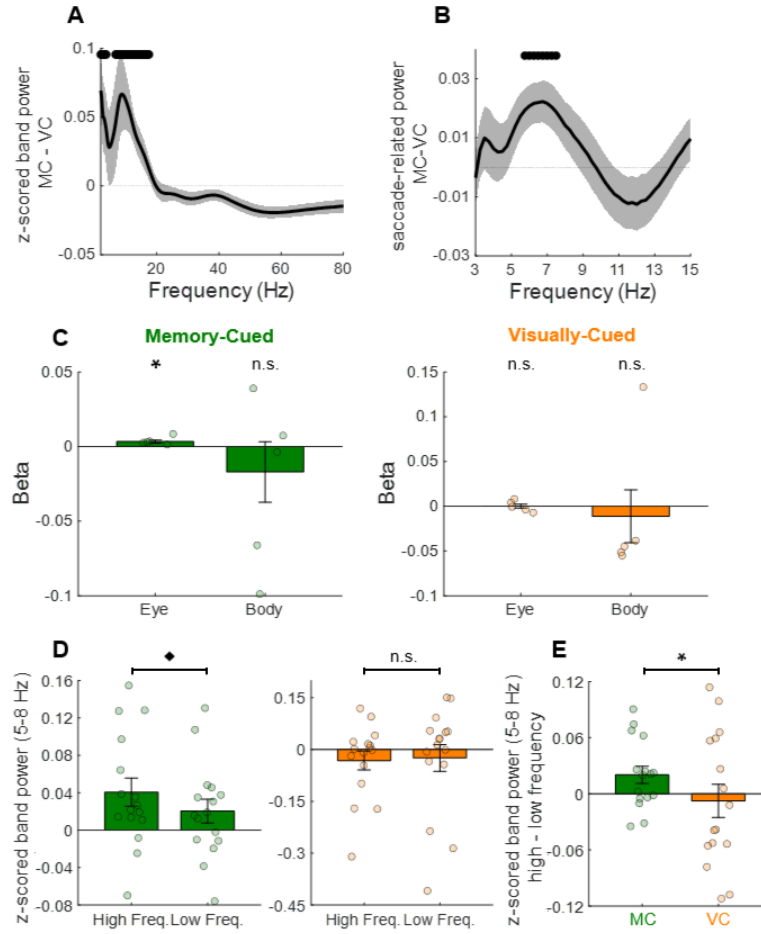
Supplementary Figure 1.1. Saccade characteristics and oscillatory prevalence. (A) Example two-second segment showing eye velocity and saccade index. (B) Distribution of saccade and fixation durations (ms) across participants ($n_{\text{participants}} = 5$). (C) Prevalence of oscillations (%). Oscillatory bouts were detected for frequency steps between 4 and 25 Hz during memory-cued and visually-cued navigation. Shaded gray area represents SEM across channels ($n_{\text{channels}} = 16$). (D) No significant differences in saccade metrics between memory-cued (MC) and visually-cued (VC) conditions: mean duration ($p = 0.47$), frequency ($p = 0.15$), displacement ($p = 0.31$), or fixation duration ($p = 0.18$). (E) Similarly, saccade metrics did not differ across performance levels. Mean saccade duration, frequency, displacement, and fixation duration did not differ significantly between HP, MP, and LP trials (all $p > 0.13$). n.s. = not significant.



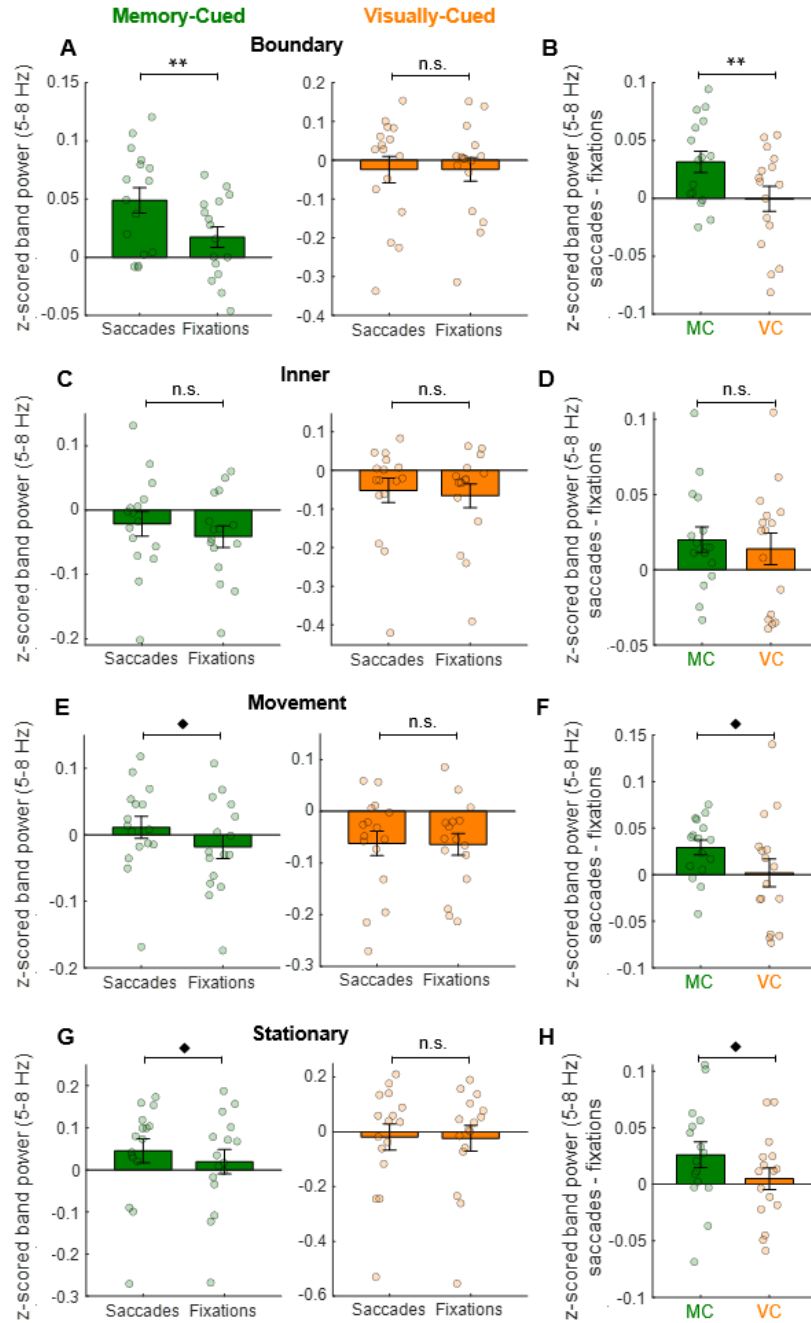
Supplementary Figure 1.2. Saccade-related theta modulation differs between planning and execution phases of memory-cued trials. (A-C) For memory-cued (MC) navigation, each trial was divided into equal first-half (planning) and second-half (execution) epochs. Normalized (z-scored) theta (5-8 Hz) activity was significantly higher during saccades compared to fixations in the first half (* $p = 0.013$; A), but not in the second half (n.s., $p = 0.254$; B). The difference in saccade-fixation theta modulation between halves was significant (* $p = 0.041$; C). (D-F) In the visually-cued (VC) navigation condition, no saccade-fixation differences were observed in the first half (n.s., $p = 0.546$; D), second half (n.s., $p = 0.327$; E) or their difference (n.s., $p = 0.772$; F). (G-H) Movement speed increased from planning to execution in both MC navigation (* $p = 0.030$; G) and visually-cued navigation (* $p = 0.031$; H), confirming greater locomotor engagement in the latter half of each trial. n.s. = not significant.



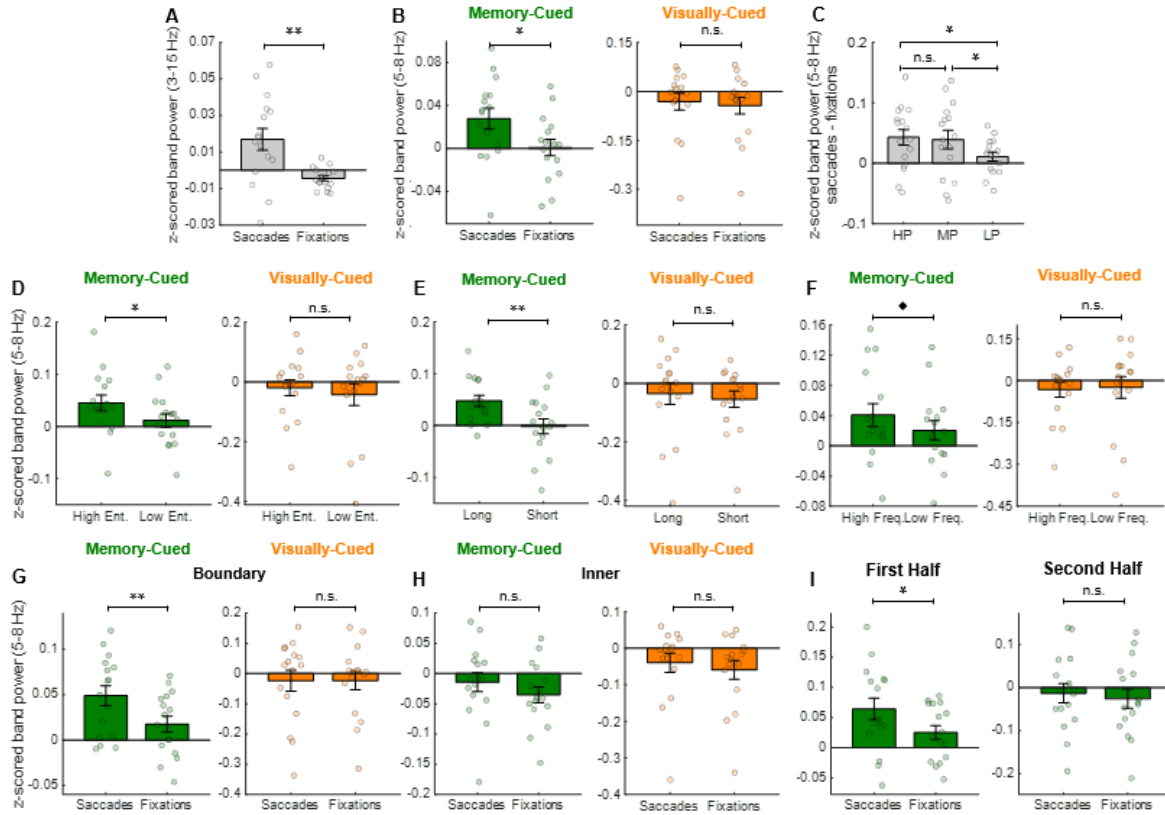
Supplementary Figure 1.3. Theta phase resetting to saccade onset. (A–B) Theta phase resetting relative to saccade onset, quantified using pairwise phase consistency (PPC). PPC was significantly elevated from –60 to +196 ms around saccade onset (black bar = $p < 0.05$, shaded areas represent SEM across participants; A), and PPC during the saccade-onset window (–50 to +200 ms) was significantly higher than an equivalently sized baseline period (–800 to –550 ms, ** $p < 0.01$; B). (C–F) Time-resolved PPC traces (mean $\pm$ SEM across participants, shaded gray) show significant theta phase alignment surrounding saccade onset in both memory-cued (MC) and visually-cued (VC) navigation. (G–J) When trials were divided into early and late halves, significant PPC increases were observed around saccade onset in both periods, indicating consistent phase resetting throughout the trial. Bar plots adjacent to each panel display mean PPC during the saccade-onset window (–50 to +200 ms) and a baseline window (–800 to –550 ms). PPC was significantly higher during the saccade period for all comparisons (** $p < 0.01$). These results demonstrate that theta phase alignment accompanies saccadic events across both task conditions and throughout the course of navigation.



Supplementary Figure 1.4. Saccades associated with memory-related theta oscillations. (A) MTL low-frequency power was elevated during memory-cued navigation compared to visually-cued navigation within the 2.0-3.75 Hz and 6.75-17.5 Hz ranges ($p < 0.05$). (B) The saccade-related oscillatory effect, characterized by an increase in band power during saccades, was more pronounced during memory-cued than during visually-cued navigation, particularly in the theta frequency range (5.75-7.5 Hz). (C) A linear mixed-effects model was employed to assess the concurrent impact of eye and body movement on theta band power, separately for memory- and visually-cued navigation. In memory-cued navigation, eye movement speed significantly contributed to theta power ($p = 0.032$), whereas body movement speed did not ($p = 0.818$). In visually-cued navigation, neither eye movement speed ($p = 0.436$) nor body movement speed ($p = 0.656$) appeared to modulate changes in theta power. (D) During memory-cued navigation, theta (5-8 Hz) power in the MTL trended higher during high- versus low-saccade frequency periods ($p = 0.096$). During visually-cued navigation, theta power in the MTL did not significantly differ between high- and low-saccade frequency periods ($p = 0.630$). (E) Comparison of the high-low entropy theta difference between memory-cued and visually-cued conditions revealed a significant interaction ($p = 0.049$). For A,B shaded gray = standard error of the mean (SEM) across channels ($n_{\text{channels}} = 16$). Black horizontal bars = $p < 0.05$. C shows mean ($\pm$ SEM) across 5 participants (circles). D,E shows mean ($\pm$ SEM) across 16 channels (circles). ♦ = $p < 0.1$, * = $p < 0.05$, n.s. = not significant.



Supplementary Figure 1.5. Control analyses for saccade-related modulation of theta band power. Normalized (z-scored) MTL theta power during saccades is shown separately for memory-cued and visually-cued conditions, in addition to direct comparisons between memory-cued and visually-cued conditions, under four behavioral contexts: (A-B) near boundaries (< 1.2 m from the wall), (C-D) inner region (> 1.2 m from the wall), (E-F) during movement, and (G-H) while stationary. Saccade-related theta increases were observed primarily during memory-cued navigation, with a significant effect near boundaries and trends in the other contexts. Each point reflects a single MTL channel (N = 16); bars represent mean $\pm$ SEM. ◆ = $p < 0.1$, ** = $p < 0.01$, n.s. = not significant.



Supplementary Figure 1.6. Analyses with increased temporal resolution. All primary analyses were repeated using BOSC parameters optimized for higher temporal resolution at the expense of frequency resolution. The results remained consistent with the main findings. **(A)** MTL low-frequency (3–15 Hz) power was significantly higher during saccades than fixations ($p = 0.001$), replicating Figure 1.2B. **(B)** During memory-cued (MC) navigation, MTL theta (5–8 Hz) power increased during saccades relative to fixations ($p = 0.013$), replicating Figure 1.3A; no significant theta increase was observed during visually-cued (VC) navigation ($p = 0.258$), consistent with Figure 1.3D. **(C)** Within MC trials, theta power increases were stronger during high-performance (HP; $p = 0.012$) and medium-performance (MP; $p = 0.035$) trials compared to low-performance (LP) trials, consistent with Figure 1.3H. **(D)** Theta power was higher during high- versus low-entropy periods in MC navigation ($p = 0.023$) but not during VC navigation ($p = 0.158$), replicating Figure 1.4E-F. **(E)** Theta power was higher during long versus short saccades in MC navigation ($p = 0.004$) but not during VC navigation ($p = 0.205$), replicating Figure 1.4B. **(F)** Theta power showed a trend toward being higher during high- versus low-frequency saccades in MC navigation ($p = 0.096$) but not during VC navigation ($p = 0.630$), replicating Supplementary Figure 1.4D. **(G)** Theta power was higher during saccades compared to fixations in boundary regions during MC navigation ($p = 0.007$) but not during VC navigation ($p = 0.506$), replicating Supplementary Figure 1.5A. **(H)** Theta power did not differ between saccades and fixations in inner-room regions for either MC or VC navigation (MC, $p = 0.130$; VC, $p = 0.164$), replicating Supplementary Figure 1.5C. **(I)** Theta power was higher during saccades compared to fixations during the first half of MC trials ($p = 0.013$) but not during the second half ($p = 0.251$), replicating Supplementary Figure 1.2A-B. All panels show mean $\pm$ SEM across 16 MTL channels (circles). * $p < 0.05$, ** $p < 0.01$, ♦ $p < 0.1$; n.s. = not significant.

Participant	Trials Completed (per condition)	Saccades/Fixations (MC)	Saccades/Fixations (VC)
P1	36	3,160	579
P2	125	3,175	1,847
P3	156	4,829	2,170
P4	147	5,426	3,234
P5	151	3,874	1,718

Supplementary Table 1.1. Number of completed trials and saccade and fixation counts per participant and condition. Values indicate the total number of trials, saccades, and fixation periods included in the memory-cued (MC) and visually-cued (VC) conditions for each participant.

Participant		1	2	3	4	5
Age		49	52	34	33	31
Gender		Female	Female	Male	Male	Male
Electrode 1	# of MTL channels	2	2	1	2	2
	Channel 1 localization	Sub/Sub	Sub/Sub	ERC/PRC	HPP/Sub	HPP/HPP
	Channel 2 localization	HPP/PWM	HPP/PRC		Sub/Sub	HPP/Sub
Electrode 2	# of MTL channels	1	2	1	2	1
	Channel 1 localization	HPP/PRC	HPP/HPP	Sub/PRC	HPP/Sub	Sub/PWM
	Channel 2 localization		HPP/HPP		Sub/Sub	

Supplementary Table 1.2. Channel localization across participants. Localization of two electrode contacts (+/−) per bipolar recording channel. HPP, hippocampus (CA1/CA2/CA3/DG); PRC, perirhinal cortex; PWM, parahippocampal white matter; Sub, subiculum; ERC, entorhinal cortex.

Chapter 2

Medial Temporal Lobe Oscillations Encode Conflict and Risk during Naturalistic Decision-Making in Freely Moving Humans

Abstract

Real-world decision-making often involves simultaneously pursuing rewards and avoiding threats, an adaptive balance essential for daily tasks such as driving, navigating crowds, or playing sports. To investigate the neural mechanisms underlying such behaviors, we studied decision-making under threat and reward uncertainty in freely moving humans. Nine participants with treatment-resistant epilepsy and implanted with Responsive Neurostimulation (RNS®) devices navigated a physical arena to collect target objects for monetary gain while avoiding a mobile experimenter who imposed monetary penalties if participants came within 1.5 meters. Trial types varied in reward-to-risk ratios to induce different levels of approach-avoidance conflict, with “High-conflict” trials defined by intermediate ratios. Behavioral results revealed systematic changes in target acquisition rates, collision frequency, trajectory detours, and spatial hesitation across trial types. A double dissociation was observed within the medial temporal lobe: low-frequency (2–3 Hz) amygdala activity preferentially tracked environmental risk, whereas low-frequency (1–8 Hz) hippocampal activity preferentially tracked approach–avoidance conflict. These context-dependent signals were further modulated by moment-to-moment behavior, emerging most strongly during active, goal-directed movement and varying across behavioral states in the hippocampus but not the amygdala. This work extends prior findings from constrained and stationary paradigms to naturalistic human behavior, and highlights medial temporal lobe oscillations as candidate biomarkers for adaptive and maladaptive decision-making in real-world settings.

2.1 Introduction

During naturalistic exploration, various aspects of an environment can lead to rewards or represent potential threats. To make appropriate behavioral responses in such situations, complex neural computations are necessary (Bryant & Barker, 2020; Ito & Lee, 2016; Roelofs & Dayan, 2022). The simultaneous avoidance of threats and pursuit of goals is necessary for advanced behaviors such as driving or walking in a crowded environment. Successful decision-making during navigation can be disrupted by conditions defined by excessive threat response, such as post-traumatic stress disorder (PTSD), or biased by reward imbalance states as in addiction (Cha et al., 2016; Kräplin et al., 2025; Mogg et al., 2005; Weaver et al., 2020).

The hippocampus and surrounding MTL structures have been linked to both spatial and non-spatial cognitive processes (Abivardi et al., 2020; Gray, 1982). Traditionally, the hippocampus has been associated with memory consolidation, movement, and the formation of cognitive maps (Buzsáki & Moser, 2013; Epstein et al., 2017). However, it also plays a crucial role in processing stimuli associated with aversive experiences and decision-making involving avoidance and pursuit (Bach et al., 2014; Davidson & Jarrard, 2004; Amsel, 1993; Jimenez et al., 2018; Schumacher et al., 2016; Godino et al., 2023; Ito & Lee, 2016; Bryant & Barker, 2020). In stationary humans, both hippocampal theta power and fMRI BOLD activity in the anterior hippocampus rise during response conflict, which may represent pattern separation and recognition of contextual deviations, ultimately leading to behavioral inhibition (Gray, 1982; Oehrns et al., 2015). These observations suggest that the hippocampus integrates reward- and risk-related information to facilitate navigation and inform valence-based decision-making in downstream brain structures (Lisman et al., 2017; Sosa & Giocomo, 2021). In both rodents and clinical accounts of human hippocampal pathology, lesions of the anterior/ventral hippocampus result in increased compulsive-like

behaviors and a decline in task performance (Bach et al., 2019a; Bryant & Barker, 2020; Cao et al., 2022; Ramm et al., 2020). Overall, the hippocampus plays a crucial role in regulating impulsivity and coordinating avoidance behaviors, particularly in situations involving motivational conflict (Çavdaroglu et al., 2021; Ito & Lee, 2016; Loh et al., 2016; Schumacher et al., 2016).

Mechanisms governing avoidance and pursuit also rely on the intricate interplay between the hippocampus and amygdala (Clauss et al., 2015; Fanselow & Hoffman, 2024; Huff et al., 2016; Jacinto et al., 2016). For instance, the remapping of rodent place cells triggered by aversive stimuli could be prevented by prior lesioning of the amygdala, indicating that the consolidation of fear and the instability of hippocampal spatial representations are contingent on amygdalar signaling (Felix-Ortiz et al., 2013; Huff et al., 2016; Kim et al., 2015). In stressed rats experiencing task conflict, elevated theta power in both the ventral hippocampus and basolateral amygdala predicted subsequent avoidance behaviors (Jacinto et al., 2016). In stationary humans performing an approach–avoidance task, risky approach was associated with coordinated increases in theta activity across the hippocampus, amygdala, and medial prefrontal cortex (Staveland et al., 2026).

While previous studies have identified brain regions supporting navigation, fear, and decision-making, ecologically valid paradigms are required to determine which aspects of human navigation drive the neural dynamics observed during approach–avoidance behavior. Fortunately, recent advancements in intracranial recording technologies enable such investigations (Stangl et al., 2023; Topalovic et al., 2020, 2023). In this study, we utilized rare access to iEEG recordings to investigate oscillatory dynamics of avoidance, pursuit, and approach-avoidance conflict in freely-moving humans. In addition, this study utilized wearable technologies including augmented reality (AR) and sub-millimeter resolution motion tracking. Participants were asked to 1) navigate

to spatial targets in AR and 2) simultaneously maintain a set distance from a freely-moving human experimenter. This required participants to continuously track another individual, incorporate reward and threat context, and dynamically adjust their navigation trajectories accordingly.

2.2 Behavioral Modulation across Approach-Avoidance Contexts

Nine individuals with pharmacoresistant epilepsy and surgically implanted with the RNS System (NeuroPace Inc., Mountain View, CA) in the medial temporal lobe participated in this study (Figure 2.1A-B). All nine participants had hippocampal recordings, of which five had additional amygdala recordings. Participants performed a freely moving approach–avoidance navigation task in augmented reality requiring them to reach a reward (treasure chest) while avoiding penalties incurred by moving within 1.5m of a moving experimenter (Figure 2.1C-E). This task required continuous spatial tracking and dynamic adjustment of movement to balance reward pursuit and threat avoidance.

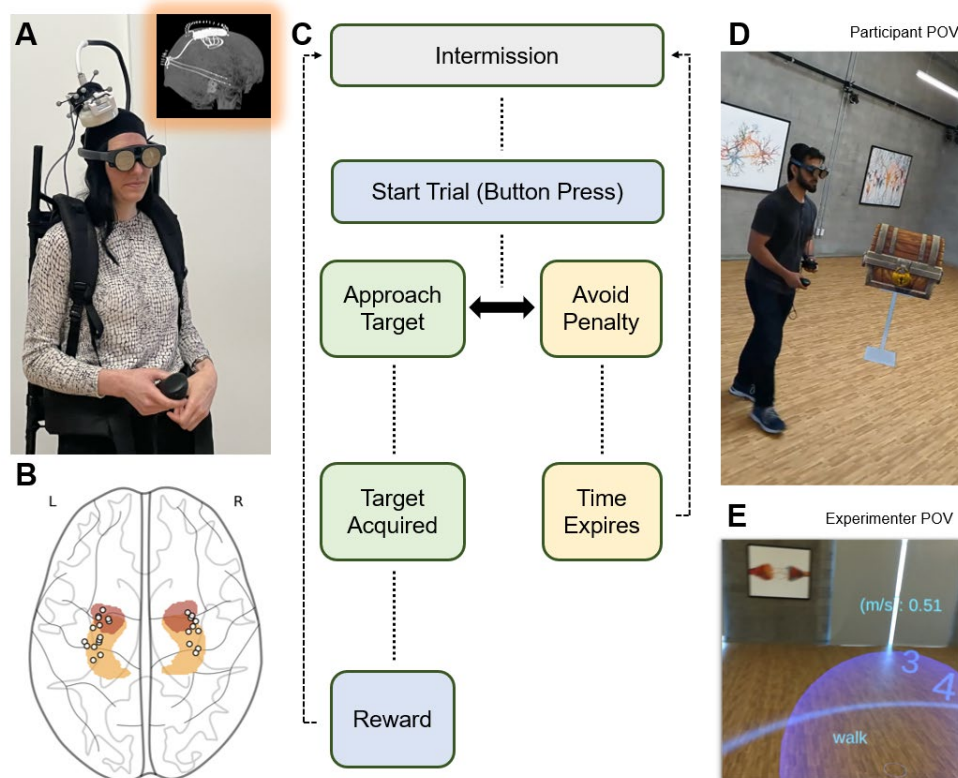


Figure 2.1. Experimental design and task. (A) Experimental setup. Participants wore a Magic Leap 2 augmented reality (AR) headset and a mobile deep brain recording system to enable wireless recording from the implanted RNS device during free movement. Inset: CT reconstruction showing the RNS device and bilateral hippocampal electrodes in an example participant. (B) Electrode localization. Schematic of the amygdala and hippocampus with all electrode contacts pooled across participants. (C) Task Structure. Each trial began with an intermission period displaying upcoming reward and penalty, as well as cumulative score. Participants could reposition freely during intermission. A button press started the trial, revealing a treasure chest (reward target). Participants navigated to reach the target while avoiding the moving experimenter, and trials ended upon target acquisition or after a time limit. (D) Participant point of view. Virtual task elements were overlaid onto the real-world environment, including the moving experimenter and treasure chest. (E) Experimenter point of view. The experimenter also wore augmented reality, and followed a predefined trajectory using a visual cue (blue sphere) with speed feedback (0.5 m/s). The experimenter was blind to task events.

Trials lasted up to 15 seconds and varied in reward and penalty magnitude, resulting in four conditions (Supplementary Table 2.1): high-risk (low reward, high penalty), high-reward (high reward, low penalty), high-conflict (moderate reward and penalty), and control (reward without penalty). These conditions created distinct motivational contexts for evaluating neural dynamics during navigation. More details regarding task structure can be found in 2.10 Methods.

Participant behavior varied systematically across these four trial types, reflecting individuals' sensitivity to the underlying risk-reward task structure. When data were pooled across trials and participants, trials with higher risk were associated with reduced approach behavior and increased avoidance behavior. For example, the percentage of trials in which participants reached the target was higher in high-reward ($94.6\% \pm 2.0\%$) and control ($94.4\% \pm 2.6\%$) conditions compared to high-risk ($73.6\% \pm 4.9\%$) and high-conflict ($84.9\% \pm 3.3\%$) conditions ($N_{\text{participants}} = 9$; all pairwise comparisons: $z > 2.55$, $p < 0.012$, FDR-corrected; Figure 2.2A). Furthermore, target acquisition was higher in high-conflict compared to high-risk trials ($z = 2.31$, $p = 0.023$; FDR-

corrected; Figure 2.2A). At the same time, the percentage of trials in which participants collided with the mobile experimenter was lower in high-risk ($2.1\% \pm 1.0\%$) than in high-reward ($10.3\% \pm 2.8\%$) and control ($25.2\% \pm 6.7\%$) conditions (both pairwise comparisons: $z = 2.55$, $p = 0.039$; FDR-corrected; Figure 2.2B). This collision rate was also lower in high-conflict ($3.6\% \pm 0.9\%$) than in control conditions ($z = 2.31$, $p = 0.039$; FDR-corrected; Figure 2.2B).

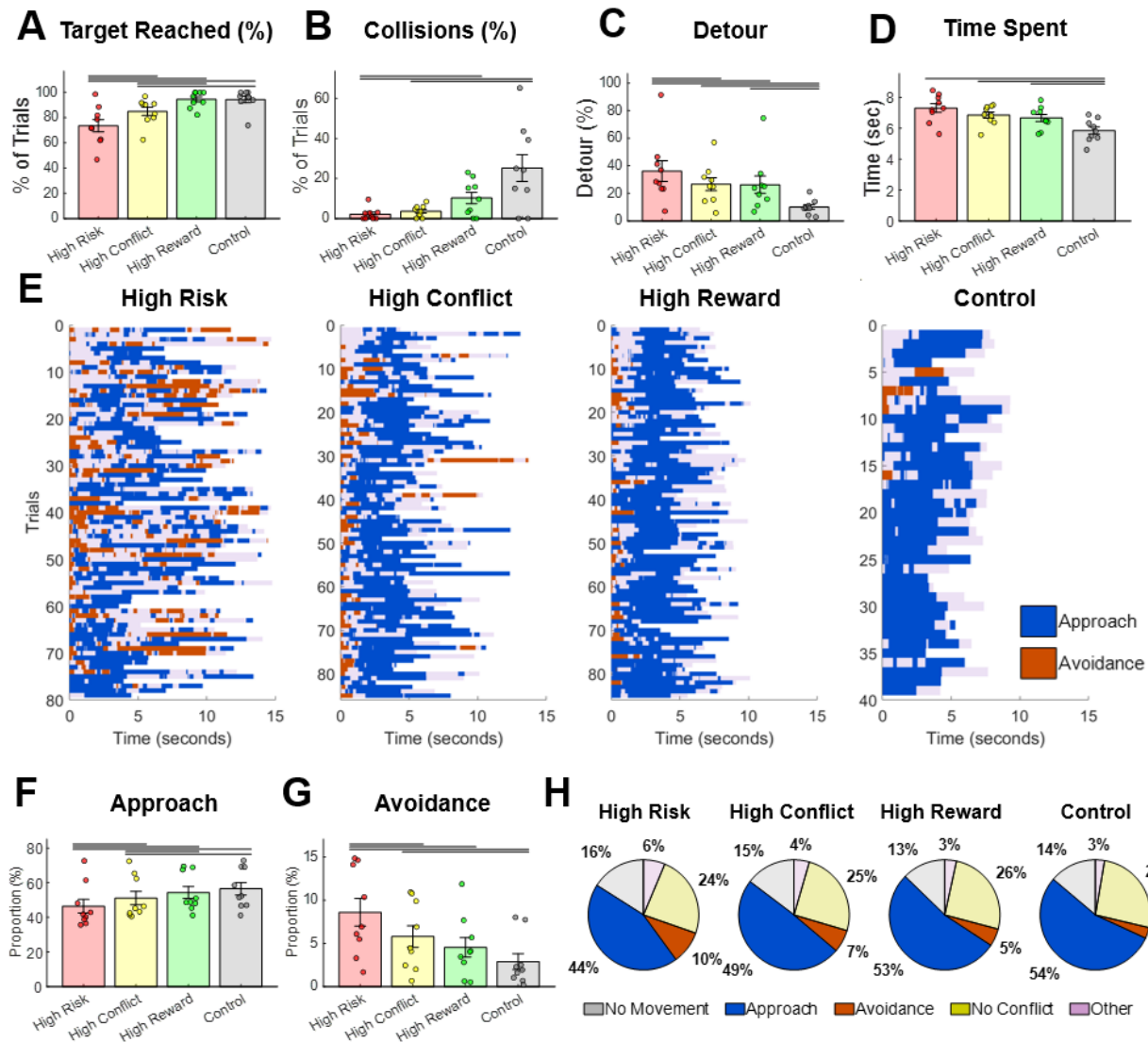


Figure 2.2. Behavioral adaptations across approach-avoidance trial types. (A–B) Task performance varied with risk level. In lower risk conditions, participants reached the target more frequently (A) and collided more with the

experimenter **(B)**. **(C–D)** Navigation strategy shifted with increasing risk. Participants exhibited greater detour **(C)** and longer trial durations **(D)** in higher-risk conditions, suggesting more cautious and indirect movement. **(E)** Example behavioral raster from a single participant, displaying moment-to-moment behavioral states across all trials and conditions. **(F–G)** Behavioral quantification. Participants spent less time in approach behavior **(F)** and more time in avoidance behavior **(G)** as the trial type risk increased. **(H)** Venn-diagram distribution of behavioral states across trial types. Approach behavior increased and avoidance behavior decreased from high-risk to control conditions. Black lines above bar plots indicate statistically significant differences ($p < 0.05$; FDR corrected).

Next, we examined whether participants exhibited greater detour during successful trials, defined as the percentage increase in path length relative to the shortest path to the target. Greater detour reflects indirect navigation, increasing time to target and potentially risking forfeit of the reward due to time constraints. Detour was elevated in high-risk ($36.2\% \pm 7.5\%$) compared to high-conflict ($26.6\% \pm 4.7\%$), high-reward ($26.3\% \pm 6.3\%$), and control ($10.1\% \pm 1.7\%$) conditions (all pairwise comparisons: $z > 2.07$, $p < 0.047$, FDR-corrected; Figure 2.2C). Detour was also lower in control trials relative to all other conditions (all pairwise comparisons: $z = 2.67$, $p = 0.008$, FDR-corrected; Figure 2.2C). We next assessed trial duration to directly determine whether these increases in detour were associated with increased time expenditure. Time to trial completion was shorter in control trials ($5.8 \text{ s} \pm 0.2 \text{ s}$) compared to high-risk ($7.3 \text{ s} \pm 0.3 \text{ s}$), high-conflict ($6.9 \text{ s} \pm 0.2 \text{ s}$), and high-reward ($6.7 \text{ s} \pm 0.2 \text{ s}$) conditions (all pairwise comparisons: $z = 2.54$, $p = 0.016$, FDR-corrected; Figure 2.2D). Together, these results indicate that increasing punishment contingencies leads participants to adopt more circuitous and time-consuming trajectories, consistent with cautious, avoidance-leaning navigation strategies.

To characterize the range of approach- and avoidance-related behaviors within each trial and how these varied across task conditions, we defined behavior at each time point based on participants' movement relative to the target and experimenter. Specifically, we determined

whether participants were moving closer to or farther from the target, and simultaneously whether they were moving closer to or farther from the experimenter. Movement toward both the target and experimenter was classified as “approach,” whereas movement away from both was classified as “avoidance.” Additional behavioral categories included “no conflict,” defined as movement toward the target and away from the experimenter, and “no movement,” defined as time points with movement speed below 0.2 m/s.

The diversity of these behaviors is illustrated in a behavioral raster from an example participant, organized by trial type (Figure 2.2E). Each row represents an individual trial, and columns correspond to the four task conditions. Qualitatively, avoidance behaviors (orange) appear more prevalent in higher-risk contexts (high-risk and high-conflict), whereas approach behaviors (blue) are more prominent in lower-risk contexts (high-reward and control). To quantify these trends, the proportion of time spent per trial in each behavioral category was computed across participants (Figure 2.2F-G). Proportions were first calculated within each trial and then averaged, weighting each trial equally. The proportion of time occupied per trial in approach behavior was reduced in high-risk ($46.4\% \pm 4.0\%$) compared to high-conflict ($51.1\% \pm 3.8\%$), high-reward ($54.3\% \pm 3.5\%$), and control ($56.5\% \pm 3.6\%$) conditions (all pairwise comparisons: $z > 2.31$, $p < 0.029$, FDR-corrected; Figure 2.2F), and was also reduced in high-conflict compared to high-reward and control conditions (both pairwise comparisons: $z > 2.07$, $p < 0.047$, FDR-corrected; Figure 2.2F). In contrast, the proportion of time spent per trial in avoidance behavior was elevated in high-risk ($8.6\% \pm 1.6\%$) relative to high-conflict ($5.8\% \pm 1.3\%$), high-reward ($4.5\% \pm 1.1\%$), and control ($2.9\% \pm 0.9\%$) conditions (all pairwise comparisons: $z > 2.55$, $p < 0.012$, FDR-corrected; Figure 2.2G), and was similarly elevated in high-conflict compared to control conditions ($z = 2.55$, $p = 0.012$, FDR-corrected; Figure 2.2G).

Finally, we visualized the relative distribution and overlap of behavioral categories across trial types using Venn diagrams (Figure 2.2H), pooling data across participants. In this analysis, proportions were computed across all timepoints within each trial type prior to averaging across participants, rather than on a per-trial basis. The proportion of ‘approach’ behavior increased progressively from High Risk to High Conflict to High Reward to Control (44% to 54%), whereas ‘avoidance’ behavior showed the opposite trend (10% to 3%). Together, these findings demonstrate that moment-to-moment behavioral choices are systematically biased by the trial context.

2.3 Dissociable Encoding of Risk and Conflict in the Amygdala and Hippocampus

Having established behavioral differences across approach-avoidance trial types, we next asked whether neural activity similarly distinguishes between these conditions. Because our primary interest was in the encoding of risk and approach-avoidance conflict, we focused on high-risk and high-conflict conditions. To enable comparison across trial types, time–frequency decomposition was performed for each recording block (Lilly & Olhede, 2012), and power values during active trial periods were normalized by z-scoring within each frequency. Data were pooled separately across hippocampal and amygdala channels, and analyses were conducted at the channel level. One-sided statistical testing was performed at each frequency step using the PALM framework, which accounts for non-independence across channels while maintaining statistical power (Winkler et al., 2014).

To start, we examined condition-related differences in normalized power across frequencies by pooling data across active trial periods and comparing high-risk and high-conflict conditions to the control condition. In the amygdala, significant increases in power were observed for both high-risk trials and high-conflict trials at 2–2.25 Hz ($N_{\text{participants}} = 5$; all comparisons: $t >$

2.17, $p = 0.034$, FDR-corrected; Figure 2.3A). These findings led us to focus our analysis on the 2–3 Hz frequency range for amygdala encoding of trial context.

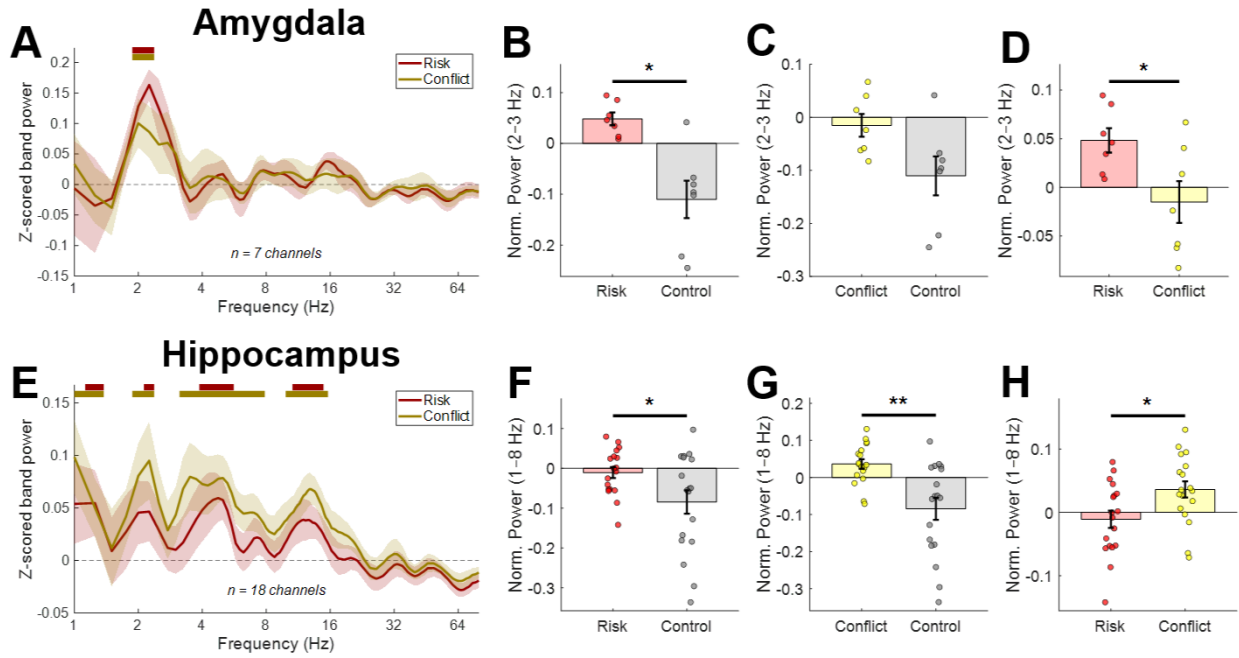


Figure 2.3. Dissociable encoding of risk and conflict in the amygdala and hippocampus. (A) Time-frequency analysis demonstrated increased low-frequency amygdala power for both high-risk and high-conflict trials relative to control. (B–D) Within the 2–3 Hz band, amygdala activity was elevated in high-risk compared to control (B), but not high-conflict vs control (C). Amygdala activity was greater in high-risk than high-conflict trials (D), indicating a preference for encoding high risk. (E) In the hippocampus, condition-related power increases for high risk and high conflict trials were broader across low frequencies. (F–H) Within the 1–8 Hz band, hippocampal activity was elevated for both high-risk (F) and high-conflict (G) trials relative to control. There was significantly greater activity in high-conflict than high-risk trials (H), suggesting preferential encoding of approach–avoidance conflict over risk. These results collectively demonstrate a double dissociation in medial temporal lobe encoding of trial context. Red and yellow horizontal lines above line charts represent statistically significant differences (FDR corrected) for high risk and high conflict trials, respectively. Black lines above bar plots indicate statistically significant differences (FDR corrected). * = $p < 0.05$, ** = $p < 0.01$.

Direct comparisons within this band confirmed that 2–3 Hz amygdala power was significantly elevated during high-risk trials compared to control ($t = 4.64$, $p = 0.010$, FDR-corrected; Figure 2.3B). In contrast, the increase observed during high-conflict trials did not reach statistical significance ($t = 1.90$, $p = 0.083$, FDR-corrected; Figure 2.3C). Furthermore, direct comparison between high-risk and high-conflict trials revealed significantly greater activity during high-risk trials ($t = 2.47$, $p = 0.042$, FDR-corrected; Figure 2.3D). Together, these results indicate that low-frequency amygdala activity, particularly in the 2–3 Hz range, preferentially tracks risk rather than approach-avoidance conflict.

We next performed a parallel analysis in the hippocampus. In contrast to the more frequency-specific effects observed in the amygdala, the hippocampus exhibited broader increases in low-frequency power across conditions. High-risk trials showed significant elevations at 1.25 Hz, 2.25 Hz, 4–5.5 Hz, and 10.75–14.75 Hz, while high-conflict trials showed elevations at 1–1.25 Hz, 2–2.25 Hz, 3.25–7.75 Hz, and 10–15.5 Hz ($N_{\text{participants}} = 9$; all comparisons: $t > 1.74$, $p < 0.05$, FDR-corrected; Figure 2.3E). These findings motivated a focused analysis of the 1–8 Hz frequency range as the candidate band for hippocampal encoding.

Within this band, 1–8 Hz hippocampal power was significantly elevated during both high-risk ($t = 2.38$, $p = 0.022$, FDR-corrected; Figure 2.3F) and high-conflict trials ($t = 3.91$, $p = 0.002$, FDR-corrected; Figure 2.3G) relative to control. Importantly, direct comparison between the two conditions revealed significantly greater activity during high-conflict compared to high-risk trials ($t = 2.24$, $p = 0.024$, FDR-corrected; Figure 2.3H). Together, these results demonstrate a double dissociation in MTL activity: low-frequency amygdala activity preferentially encodes risk, while low-frequency hippocampal activity preferentially encodes approach-avoidance conflict.

2.4 Trial Context Encoding is Specific to Target Approach

We next examined whether medial temporal lobe (MTL) encoding of trial context was specific to particular behaviors during approach–avoidance navigation. Given that amygdala modulation was strongest in high-risk contexts and localized to the 2–3 Hz range, we analyzed this effect separately across three moment-to-moment behavioral states: no movement, approach, and no conflict (as defined in Section 2.2). The ‘avoidance’ behavior was excluded for this analysis due to small sample size (e.g. Figure 2.2G-H). Based on the presence of a priori directional hypotheses confirmed by Section 2.3, all PALM statistical tests were conducted as one-sided.

Within the amygdala, 2–3 Hz activity during high-risk, high-conflict, and control trials did not differ during periods of no movement ($N_{\text{participants}} = 5$; all pairwise comparisons: $t < 1.44$, $p > 0.213$, FDR-corrected; Supplementary Figure 2.1A). In contrast, significant increases in high risk relative to high-conflict and control trials were observed during approach behavior (both pairwise comparisons: $t < 2.05$, $p > 0.042$, FDR-corrected; Supplementary Figure 2.1B). Furthermore, significant increases in high risk relative to control trials were observed during no-conflict periods ($t = 4.82$, $p = 0.010$, FDR-corrected; Supplementary Figure 2.1C).

We performed a parallel analysis in the hippocampus, focusing on high-conflict trials and the 1–8 Hz frequency range, where modulation was most pronounced. Hippocampal 1–8 Hz activity during high-conflict trials did not differ from control during no-movement periods ($N_{\text{participants}} = 9$; all pairwise comparisons: $t < 0.98$, $p > 0.279$, FDR-corrected; Supplementary Figure 2.1D). However, significant increases relative to control were observed for high-risk and high-conflict trials during approach behavior (both pairwise comparisons: $t > 2.35$, $p < 0.025$, FDR-corrected; Supplementary Figure 2.1E). Additionally, significant increases were noted for high-conflict compared to high-risk and control trials during the “no-conflict” behavior (both

pairwise comparisons: $t > 2.94$, $p < 0.007$, FDR-corrected; Supplementary Figure 2.1F). Together, these findings indicate that MTL encoding of trial context is behaviorally selective, as amygdala and hippocampal modulation primarily emerges when the participant moves closer to the target, rather than during immobility.

2.5 Hippocampus, Not Amygdala, Encodes Within-Trial Behavioral States

Next, we investigated whether the amygdala and hippocampus encode specific behaviors within the course of a trial. To address this, we compared neural activity across three behavior states (no movement, approach, and no conflict) within each brain region and trial type. All statistical tests were conducted using two-sided PALM analyses, as no a priori hypotheses predicted the direction of effects.

In the amygdala, no differences in 2–3 Hz activity were observed across behavior states in any trial condition. In the high-risk condition, activity did not differ among the three behaviors ($N_{\text{participants}} = 5$; all pairwise comparisons: $t < 0.58$, $p = 0.382$, FDR-corrected; Figure 2.4A). Similarly, no differences were observed in the high-conflict condition (all pairwise comparisons: $t < 1.05$, $p > 0.323$, FDR-corrected; Figure 2.4B) or in the control condition (all pairwise comparisons: $t < 1.86$, $p > 0.188$, FDR-corrected; Figure 2.4C).

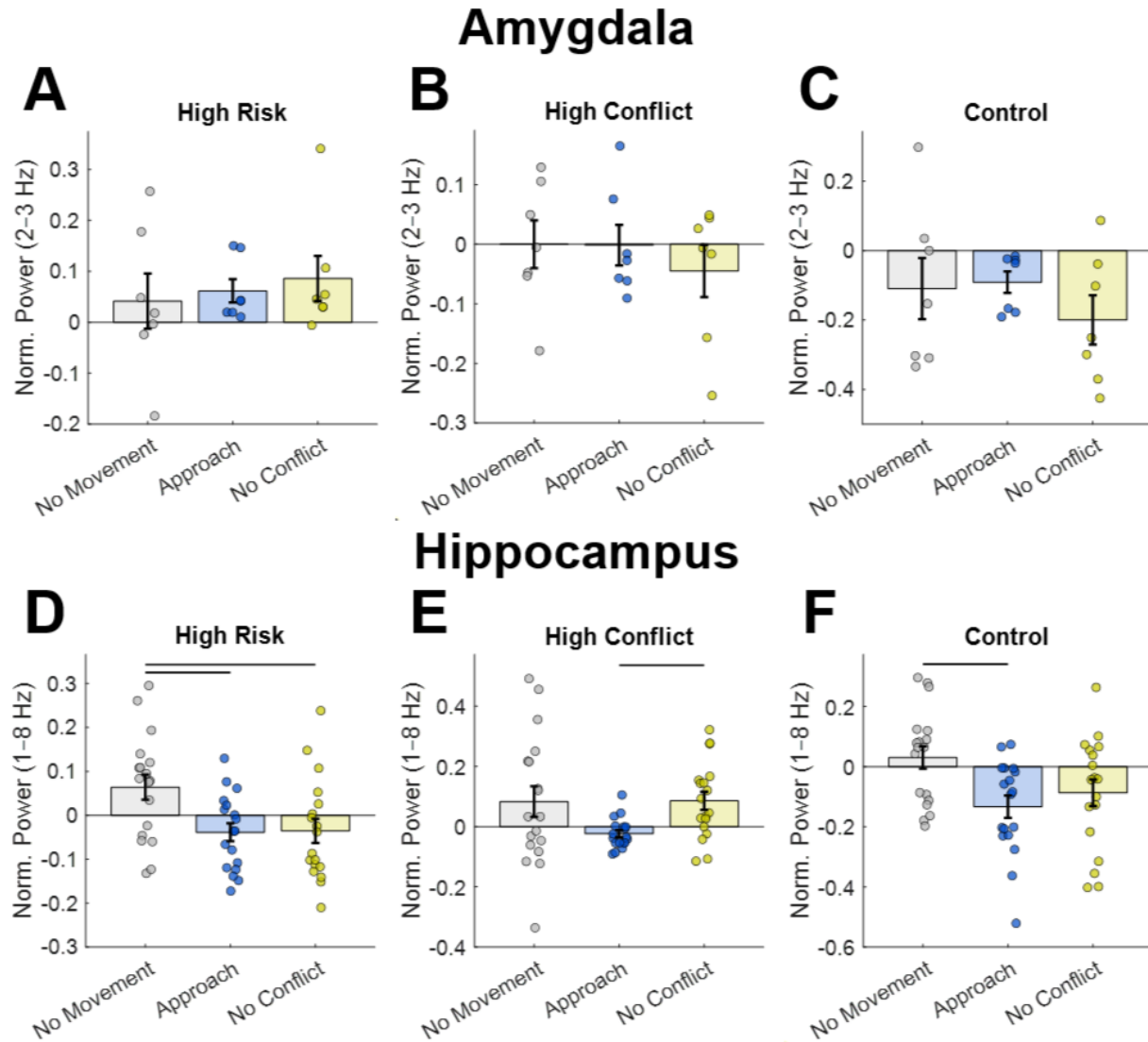


Figure 2.4. Behavioral state encoding in amygdala and hippocampus. (A–C) Amygdala 2–3 Hz activity did not differ across behavioral states (no movement, approach, no conflict) within high-risk (A), high-conflict (B), or control (C) conditions. (D–F) In contrast, hippocampal 1–8 Hz activity showed behavior-specific differences that varied by trial context. (D) In high-risk trials, activity was elevated during no-movement relative to approach and no-conflict behaviors. (E) In high-conflict trials, activity was elevated during no-conflict relative to approach. (F) In control trials, activity was elevated during no-movement relative to approach. Overall, hippocampal modulation was behaviorally selective but not consistent across contexts, while the amygdala showed no within-trial behavioral differences. Black lines above bar plots indicate statistically significant differences (FDR corrected; $p < 0.05$).

However, the hippocampus did exhibit behavior-specific modulation in the 1–8 Hz frequency range. In the high-risk condition, activity during no-movement periods was elevated relative to both approach and no-conflict behaviors ($N_{\text{participants}} = 9$; both pairwise comparisons: $t > 2.51$, $p < 0.012$, FDR-corrected; Figure 2.4D). In the high-conflict condition, activity during no-conflict periods was elevated relative to approach ($t = 4.04$, $p < 0.001$, FDR-corrected; Figure 2.4E). In the control condition, activity during no-movement periods was elevated compared to approach ($t = 3.07$, $p = 0.009$, FDR-corrected; Figure 2.4F).

Hippocampal effects did not follow an obvious pattern across trial types, as no single behavioral category was consistently associated with increased activity. Instead, modulation varied as a function of the motivational context of the trial. Notably, this contrasts with the amygdala which featured no differences across behaviors in any motivational context. Thus, hippocampal activity appears to reflect a conjunctive but context-dependent encoding of behavior, rather than a stable mapping between behavior and neural response.

2.6 Amygdala and Hippocampus Encode Reward

While the previous analyses focused on risk and approach-avoidance conflict, we subsequently examined neural responses in the high-reward condition (Reward = 1000, Penalty = 100). This condition includes a small potential penalty, and is thus not equivalent to the control condition (Reward = 500, Penalty = 0), but instead represents a context in which potential gains strongly outweigh potential losses.

For the amygdala, we first assessed condition-related differences in normalized power across frequencies by pooling data across active trial periods and comparing high-reward to control trials. Significant increases in power were observed at 1.75–2.25 Hz and 2.75–3 Hz ($N_{\text{participants}} = 5$; all comparisons: $t > 2.19$, $p < 0.046$, FDR-corrected; Supplementary Figure 2.2A), consistent

with low-frequency effects observed in other conditions. We thus focused on the 2-3 Hz frequency range. Relative to control, amygdala 2–3 Hz power was significantly elevated during high-reward trials ($t = 3.60$, $p = 0.016$, FDR-corrected; Supplementary Figure 2.2B). We then examined modulation of behavioral states within the high-reward condition, and found no significant differences across the three behavioral states analyzed (no movement, approach, no conflict; all pairwise comparisons: $t < 2.23$, $p > 0.125$, FDR-corrected; Supplementary Figure 2.2C).

We then performed an analogous analysis in the hippocampus. Comparing high-reward to control trials demonstrated significant power elevations across a broad low-frequency range, including 1–1.25 Hz, 2–2.25 Hz, 3.25–5.5 Hz, and 10.5–14.75 Hz ($N_{\text{participants}} = 9$; all comparisons: $t > 1.88$, $p < 0.041$, FDR-corrected; Supplementary Figure 2.2D). We focused on the 1–8 Hz range, consistent with our prior analyses. Relative to control, hippocampal 1–8 Hz power was significantly elevated during high-reward trials ($t = 3.01$, $p = 0.003$, FDR-corrected; Supplementary Figure 2.2E). As in the amygdala, no significant differences were observed across the three behavioral states within the high-reward condition (all pairwise comparisons: $t < 1.12$, $p > 0.301$, FDR-corrected; Supplementary Figure 2.2F).

Altogether, these findings suggest that both the hippocampus and amygdala exhibit elevated low-frequency activity in high-reward trials, but these reward-related increases do not differentiate among behavioral states.

2.7 MTL Activity is Elevated at Trial Onset

We next examined how low-frequency MTL activity evolves over the course of a trial by aligning time–frequency representations to trial onset and offset. For trial onset analyses, data were time-locked to the beginning of each trial, spanning 1 s before to 3 s after onset. For trial offset

analyses, data were aligned to trial end, spanning 3 s before to 1 s after termination. These effects were initially computed across all four trial types (high risk, high conflict, high reward, control).

In the amygdala (Supplementary Figure 2.3), low-frequency activity, particularly in the ~2–6 Hz range, was elevated prior to trial onset (warmer colors in the spectrogram) and remained modestly elevated for approximately 2 s after trial initiation before returning toward baseline (Supplementary Figure 2.3A). In contrast, when aligned to trial offset, low-frequency activity remained relatively suppressed (cooler colors) throughout the final 3 s of the trial and did not increase following trial termination (Supplementary Figure 2.3B).

To quantify these effects, we isolated the 2–6 Hz band and examined mean power within 0.5 s time bins relative to trial onset. One-sided statistical comparisons against zero were performed using the PALM framework with FDR correction (Winkler et al., 2014). Amygdala theta power was significantly elevated during the 1 s preceding trial onset ($N_{\text{participants}} = 5$; all comparisons: $t > 2.67$, $p < 0.02$, FDR-corrected) and showed a transient increase during the first 0.5 s after trial onset that did not survive FDR correction ($t = 2.66$, $p = 0.07$, FDR-corrected; Supplementary Figure 2.3C). As expected, no significant modulation was observed in the 3 s preceding or 1 s following trial offset (Supplementary Figure 2.3D).

We performed an analogous analysis in the hippocampus, which also demonstrated elevated low-frequency activity (~2–6 Hz) prior to trial onset and which remained elevated for approximately 2.5 s following trial initiation before returning toward baseline (Supplementary Figure 2.4A). As with the amygdala, these effects were averaged across all four trial types. When aligned to trial offset, low-frequency activity remained relatively low throughout the final portion of the trial and did not increase after trial completion (Supplementary Figure 2.4B). Quantification of 2–6 Hz power revealed that hippocampal theta activity was significantly elevated during the 1

s preceding trial onset and remained significantly elevated during the first 0.5 s after trial onset ($N_{\text{participants}} = 9$; all comparisons: $t > 3.58$, $p < 0.003$, FDR-corrected; Supplementary Figure 2.4C). No significant modulation was observed around trial offset (Supplementary Figure 2.4D).

Together, these findings indicate that low-frequency MTL activity is transiently elevated at trial onset, consistent with a role in anticipation or preparation, and is not similarly modulated at trial termination. We next asked whether these pre-trial effects were consistent across trial contexts or driven by specific conditions. To address this, we repeated the same analysis separately for each trial type (Supplementary Figure 2.5).

In the amygdala, 2–6 Hz activity was elevated prior to trial onset across all four trial types (Supplementary Figure 2.5A–D). Specifically, significant elevations were observed 0.5–1 s before trial onset during high-risk trials ($t = 3.13$, $p = 0.023$, FDR-corrected; Supplementary Figure 2.5A), 0–0.5 s before onset during high-conflict trials ($t = 2.30$, $p = 0.043$, FDR-corrected; Supplementary Figure 2.5B), 0–1 s before onset during high-reward trials (all comparisons: $t > 1.76$, $p < 0.044$, FDR-corrected; Supplementary Figure 2.5C), and 0–0.5 s before onset during control trials ($t = 1.80$, $p = 0.043$, FDR-corrected; Supplementary Figure 2.5D). No post-onset elevations survived FDR correction in any condition. These results indicate that pre-trial amygdala activity is consistently elevated across contexts, independent of trial type.

On the other hand, hippocampal pre-trial activity displayed a more context-dependent pattern (Supplementary Figure 2.5E–H). Significant elevations in 2–6 Hz power were observed prior to trial onset during high-risk trials (0–1 s before onset; all comparisons: $t > 3.07$, $p < 0.008$, FDR-corrected; Supplementary Figure 2.5E), high-conflict trials (0.5–1 s before onset; $t = 3.12$, $p = 0.005$, FDR-corrected; Supplementary Figure 2.5F), and high-reward trials (0–1 s before onset; all comparisons: $t > 4.47$, $p < 0.001$, FDR-corrected; Supplementary Figure 2.5G). No significant

pre-trial elevations were observed in the control condition (Supplementary Figure 2.5H). Thus, unlike the amygdala, hippocampal pre-trial activity appears to be selectively engaged in non-control contexts with risk of penalty, suggesting sensitivity to task demands that extend beyond baseline navigation.

2.8 Elevated MTL Activity During Pre-Trial Intermission Reflects Planning

The preceding analysis raised the possibility that MTL activity is elevated not only at trial onset, but broadly throughout the pre-trial intermission period. To test this, we compared frequency-resolved power during the intermission periods to that observed during active trial periods, separately for each trial type. During intermission, participants were not under immediate threat but viewed augmented reality cues providing information about the upcoming trial, such as the trial type. Although the target was not yet visible, participants could move freely within the environment, allowing for partial navigation and strategic positioning. Thus, the intermission period afforded an opportunity for anticipatory planning under incomplete trial information.

In the amygdala, intermission power was generally elevated relative to active trial power across trial types. Specifically, in high-risk trials, intermission power was elevated in the 3–5 Hz range ($N_{\text{participants}} = 5$; all comparisons: $t > 2.65$, $p < 0.035$, FDR-corrected; Supplementary Figure 2.6A, top left). In high-conflict trials, elevations were observed at 4–5 Hz (all comparisons: $t > 2.06$, $p < 0.042$, FDR-corrected; Supplementary Figure 2.6A, top right), and in high-reward trials at 3.5–5 Hz (all comparisons: $t > 2.91$, $p < 0.028$, FDR-corrected; Supplementary Figure 2.6A, bottom left). In contrast, the control condition showed elevated intermission power at higher frequencies (all comparisons: 8.75–9.75 Hz; $t > 2.88$, $p < 0.042$, FDR-corrected; Supplementary Figure 2.6A, bottom right). These findings suggest that amygdala activity during intermission is

elevated in low-frequency bands across all task conditions, potentially reflecting trial anticipation and environmental evaluation.

A similar pattern was observed in the hippocampus, where intermission power exceeded trial-period power across all conditions. In high-risk trials, elevations were observed at 1–1.75 Hz, 2.75–7.75 Hz, and 62–73 Hz ($N_{\text{participants}} = 9$; all comparisons: $t > 1.74$, $p < 0.050$, FDR-corrected; Supplementary Figure 2.6B, top left). In high-conflict trials, elevations occurred at 1–1.75 Hz and 3–7.75 Hz ($t > 1.59$, $p < 0.049$, FDR-corrected; Supplementary Figure 2.6B, top right). In high-reward trials, increases were noted at 1–2 Hz and 2.75–7.75 Hz ($t > 1.99$, $p < 0.047$, FDR-corrected; Supplementary Figure 2.6B, bottom left), and in control trials at 1–2 Hz and 3–7.75 Hz ($t > 2.27$, $p < 0.019$, FDR-corrected; Supplementary Figure 2.6B, bottom right). Interestingly, these effects were observed within the 1–8 Hz range, aligning with earlier findings implicating low-frequency hippocampal activity in encoding task context.

To determine whether intermission-related activity differs across trial types, we examined condition-related differences in normalized power during the intermission period by pooling data across time and comparing intermission activity preceding each condition (high risk, high conflict, high reward) to the control intermission. This parallels our previous analysis comparing active trial types (Supplementary Figure 2.2A,D). In the amygdala, significant increases in power were observed for high-risk intermissions at 1.25 Hz and 4–4.5 Hz, for high-conflict intermissions at 4–4.5 Hz, and for high-reward intermissions at 1.25 Hz and 4–4.5 Hz (all comparisons: $t > 1.98$, $p < 0.047$, FDR-corrected; Supplementary Figure 2.6C). These effects suggest that amygdala activity during intermission retains sensitivity to upcoming trial context, particularly within low-frequency bands.

We next performed a parallel analysis in the hippocampus. Consistent with earlier findings, the hippocampus exhibited broader increases in low-frequency power across intermission conditions. Specifically, high-risk intermissions showed significant elevations at 2.5–2.75 Hz, high-conflict intermissions at 1 Hz and 2.25–2.75 Hz, and high-reward intermissions at 1 Hz and 2.25–3 Hz (all comparisons: $t > 1.84$, $p < 0.048$, FDR-corrected; Supplementary Figure 2.6D). These results indicate that hippocampal activity during intermission is also modulated by upcoming trial context, with effects spanning a wider low-frequency range than those observed in the amygdala.

Together, these findings demonstrate that MTL activity during intermission is not only elevated overall compared to the trial, but also differentiates between upcoming trial types. This suggests that anticipatory MTL processes may encode contextual information, in addition to navigational planning, prior to trial onset.

2.9 Discussion

In this study, we investigated the neural bases of how humans navigate approach-avoidance decisions in a naturalistic, immersive environment. We found that both behavior and neural activity varied systematically as a function of the task's underlying risk-reward structure. Behaviorally, participants adopted more conservative strategies in higher-risk environments, characterized by reduced target approach, increased avoidance, and more circuitous navigation. At the neural level, we observed a double dissociation within the medial temporal lobe: low-frequency (2–3 Hz) amygdala activity preferentially tracked risk, whereas low-frequency (1–8 Hz) hippocampal activity preferentially tracked approach–avoidance conflict.

This dissociation extends prior work implicating the amygdala in threat evaluation and the hippocampus in conflict monitoring and resolution (Bryant & Barker, 2020; Godino et al., 2025; McNaughton & Gray, 2000; Staveland et al., 2026), and demonstrates that these dynamics are preserved in naturalistic, real-world navigation rather than being limited to stationary or animal-based paradigms. Importantly, these signals emerged in an environment requiring assessment of context and continuous spatial decision-making, suggesting that MTL contributions to approach-avoidance behavior generalize to ecologically valid contexts.

Moreover, these context-dependent neural signals in the amygdala and hippocampus were not uniformly expressed across time, but were gated by moment-to-moment human behavior. MTL encoding of trial context was most pronounced during active goal-directed movement, specifically during approach and no-conflict states rather than immobility. This does not imply that movement alone drives theta activity. Prior work suggests that theta is only weakly or conditionally related to movement velocity in freely behaving humans, and is instead modulated by memory demands, spatial context, and other behaviorally relevant signals such as eye movements or proximity to environmental boundaries (Seeber et al., 2025; Stangl et al., 2021; Zubair et al., 2026). Instead, our findings suggest that context-related neural signals are differentiated most during periods of active engagement.

One possibility is that immobility, which disproportionately occurs at the beginning of trials, reflects internal deliberation or planning processes that are relatively consistent across contexts, such as locating the target and forecasting a navigation route, thereby reducing detectable differences between conditions. In contrast, active movement may differentially engage these circuits depending on the underlying motivational context. For example, movement during high-

conflict trials likely entails ongoing evaluation of experimenter behavior with elevated arousal, while movement during control trials may reflect execution of relatively straightforward, low-conflict locomotion. Alternatively, movement itself may amplify underlying neural representation contrasts through enhanced environmental sampling, sensorimotor coupling, or large-scale network interactions (Adhikari et al., 2010; Almani et al., 2025; Siegel et al., 2012). Disentangling these possibilities will require future analyses that explicitly separate planning, movement execution, and environmental monitoring.

Within this framework, the amygdala and hippocampus exhibited different modes of representation. The amygdala did not differentiate between behavioral states within trials, suggesting that it encodes global contextual features, such as environmental risk, somewhat independently of ongoing behavior (Janak & Tye, 2015). In contrast, the hippocampus showed behavior-dependent modulation that varied across contexts, consistent with a flexible, conjunctive coding scheme (Barry & Doeller, 2010). Notably, hippocampal activity did not follow a consistent fixed mapping between theta activity and specific behaviors. Instead, hippocampal theta was generally lower during approach compared to no-movement states, while no-conflict behavior exhibited the greatest context-dependent variation. This variation aligns with theories that the hippocampus encodes state-dependent representations within cognitive maps (Behrens et al., 2018; Eichenbaum, 2017), while the amygdala encodes threat-related valence (Janak & Tye, 2015; Phelps & LeDoux, 2005).

A seemingly paradoxical pattern emerged in the high-conflict condition, where hippocampal activity was elevated during “no-conflict” behavior, defined as movement toward the goal while simultaneously increasing distance from the threat, compared to approach behavior.

During approach, participants moved toward both the reward and the experimenter, requiring continuous evaluation of whether to continue or abandon the trajectory. In contrast, no-conflict behavior represents a moment in which this tradeoff has been resolved, and the participant is progressing along a trajectory that satisfies both goals. Although we expected no-conflict periods to be associated with reduced hippocampal theta, given the relative absence of ongoing decision conflict, the opposite pattern was observed specifically in the high-conflict context.

One interpretation is that hippocampal theta reflects the evaluation of recently executed trajectories or refinement of behavioral strategies rather than the instantaneous presence of conflict. In this view, elevated activity during no-conflict periods may reflect an assessment of the preceding sequence of actions and events that successfully resolved competing demands. This interpretation mirrors evidence that hippocampal activity in rodents supports active evaluation and memory-based updating of behavioral paths, including replay of recently experienced trajectories (Carr et al., 2011; Foster & Wilson, 2006; Gupta et al., 2010). This interpretation also aligns with human intracranial work linking hippocampal theta to memory-guided navigation and internal sequence representation (Maoz et al., 2023; Seeber et al., 2025; Stangl et al., 2023). Under this framework, the hippocampus may transiently increase activity following successful conflict resolution to reinforce the trajectory that led to that outcome.

An alternative, but not mutually exclusive, interpretation is that suppressed hippocampal theta represents suboptimal or risky actions. In the present task, approach behavior was defined as moving toward both reward and threat, a potentially unstable trajectory. Consistent with this possibility, approach periods tended to show low hippocampal activity across conditions, although differences did not always reach statistical significance (Figure 2.4D-F). This interpretation is

broadly consistent with prior work suggesting that hippocampal engagement is reduced during impulsive behavior and enhanced during cautious or avoidance-related states (Adhikari et al., 2010; Bach et al., 2014; Gray, 1982; Ito & Lee, 2016; Schumacher et al., 2016). Additionally, while theta activity is sometimes interpreted as a proxy for arousal (Sainsbury, 1998), the double dissociation observed here, particularly that hippocampal theta encodes conflict while amygdala theta encodes risk, argue against a purely arousal-based account.

More broadly, these findings suggest that while the hippocampus reliably tracks approach–avoidance conflict at the contextual level, moment-to-moment fluctuations in activity may reflect dynamic evaluation of recently executed or ongoing trajectories rather than momentary conflict magnitude. Future analyses focusing on discrete behavioral motifs (Mobbs et al., 2021), such as experimenter turns and behavioral state transitions (e.g., approach followed by no-conflict), may help determine whether hippocampal signals are reflective of momentary behavioral state, upcoming decisions, or recently resolved conflict states.

Beyond within-trial dynamics, both the hippocampus and amygdala exhibited elevated low-frequency activity prior to trial onset and during intermission periods, suggesting a role in anticipatory processing. During the intermission phase, participants were not exposed to immediate threat but were presented with augmented reality text indicating the context of the upcoming trial. Although the target location remained unknown, participants often moved within the environment, strategically positioning and preparing for the upcoming trial. Thus, this intermission period likely supported anticipatory planning based on incomplete information about the forthcoming trial. Notably, hippocampal pre-trial theta activity was not enhanced for control intermissions, preceding trials in which experimenter tracking is less relevant, whereas amygdala

theta activity was elevated in the same pre-trial period. This dissociation affirms the hypothesis that the hippocampus is engaged selectively by context-dependent planning or simulation of future trajectories (Addis & Schacter, 2012; Behrens et al., 2018; Buckner, 2010; Johnson & Redish, 2007), whereas the amygdala reflects a more general state of vigilance or salience tracking (Janak & Tye, 2015; Pessoa & Adolphs, 2010; Phelps & LeDoux, 2005). During intermission, both regions showed elevated theta activity in high-risk, high-conflict, and high-reward conditions relative to control (Supplementary Figure 2.6), indicating amygdala salience may be further elevated when risk of penalty is involved.

These findings can be interpreted within the framework of Gray's behavioral inhibition theory, which proposes that the septo-hippocampal system detects and resolves conflict between competing goals (Gray, 1982; McNaughton & Gray, 2000). In this view, hippocampal theta interrupts ongoing behavior to facilitate evaluation and choice adjustment. Our results are consistent with this theory, as we observed elevated hippocampal theta during intermission and early trial periods. We propose that hippocampal activity may also reflect evaluation and updating of behavioral trajectories within approach-avoidance conflict. Such evaluation may occur at multiple timepoints, including during intermission (when task parameters are revealed and high-level strategies are formed), early trial immobility (when navigation is planned), and during "no-conflict" periods following successful navigation around threat. This interpretation is consistent with parallel findings from memory studies that hippocampal activity supports the encoding, retrieval, and evaluation of sequential experiences. In particular, hippocampal theta and replay dynamics have been linked to the reactivation and updating of recently experienced trajectories, as well as reinforcement of successful paths (Pfeiffer, 2020; Rudoler et al., 2023). During active behavior, theta sequences compress and organize recent experience into ordered representations,

allowing ongoing actions to be evaluated against stored trajectories, while coordinated hippocampal–prefrontal interactions support memory-guided decision-making and learning from outcomes (Zielinski et al., 2020). In humans, hippocampal theta is also modulated during successful spatial memory retrieval, further linking these signals to memory-based evaluation processes (Maoz et al., 2023). More broadly, we propose that our findings support a unifying view of the hippocampus as a dynamic evaluator of behavioral sequences in both memory and approach-avoidance conflict: a system that not only represents trajectories, but also reactivates and updates them based on recent outcomes, allowing past experience to inform ongoing and future behavior.

The study’s findings also show that hippocampal and amygdala theta were elevated in high-reward contexts, indicating that MTL function cannot be reduced to processing negative valence or approach-avoidance conflict alone. Although the high-reward condition (1000 reward, 100 penalty) appears to involve minimal conflict, the presence of even a small penalty may have been sufficient to induce continued avoidance tendencies, particularly in participants motivated to optimize outcomes. This is reflected by the findings that behavior in the high-reward condition resembled that of the high-conflict condition, with comparable detour and trial duration, and both were elevated relative to control trials. These results suggest that neural activity was not driven solely by external value contingencies, but also by participants’ internal appraisal of those contingencies and their behavioral goals. This interpretation also aligns with prior theories that both the hippocampus and amygdala are sensitive to subjective value, uncertainty, and motivational salience, rather than objective reward or threat alone (Bach et al., 2019b; Gottfried et al., 2003; Kahn et al., 2002; Phelps & LeDoux, 2005).

An important caveat is that the observed effects in the high-reward condition are difficult to attribute uniquely to reward processing. Instead, they may reflect a combination of reward anticipation and residual sensitivity to potential punishment, even when that penalty is relatively minor. This interpretation is consistent with well-established behavioral and neural evidence that humans often overweigh potential losses relative to gains (Kahneman & Tversky, 1979; Tom et al., 2007), and that even low-magnitude or low-probability threats can influence decision-making and neural responses. Future experiments that isolate pure reward conditions, without any associated penalty, will be necessary to determine whether the observed MTL activity reflects reward processing or the integration of reward and residual threat.

Although our analyses focused on the hippocampus and amygdala, these regions operate within a broader decision-making network. Medial prefrontal regions, including anterior cingulate cortex, ventromedial prefrontal cortex, and orbitofrontal cortex, are critical for integrating value signals, maintaining task representations, and guiding flexible behavior (Chu et al., 2023; Clarke et al., 2015; Gazit et al., 2020; Hiser & Koenigs, 2018; Klein-Flügge et al., 2022; Staveland et al., 2026; Wassum, 2022). In parallel, mesocorticolimbic dopaminergic circuits, including projections from the ventral tegmental area to the nucleus accumbens, amygdala, and prefrontal cortex, modulate these processes by signaling motivational salience and expected outcomes (Cox & Witten, 2019; Floresco, 2015; Hsu et al., 2005; Lammell et al., 2014). Notably, dopaminergic signaling within the hippocampus itself has been shown to regulate approach–avoidance behavior via distinct receptor pathways, suggesting a mechanistic link between valuation systems and hippocampal computations (Godino et al., 2025).

Moreover, decision-making in this task likely reflects interactions between multiple learning systems beyond the medial temporal lobe. A large body of work has demonstrated that the neostriatum supports a parallel, habit-based learning system that gradually acquires stimulus–response associations through reinforcement, distinct from hippocampal-dependent, flexible representations. In the classic probabilistic classification paradigm, patients with medial temporal lobe damage show intact habit learning, whereas patients with striatal dysfunction are impaired, revealing a double dissociation between these systems (Knowlton et al., 1996). Subsequent work has extended this framework, showing that the basal ganglia contribute to gradual, feedback-driven learning and action selection, particularly under conditions that favor repeated or stereotyped responses (Shohamy et al., 2008; Wilkinson et al., 2014). Additionally, striatal dopamine release tracks reinforcement learning signals during these probabilistic tasks. It is plausible that lower-conflict or control conditions in the present task may permit greater engagement of such habit-like strategies, whereas high-risk and high-conflict conditions require flexible, hippocampal-dependent evaluation of spatial trajectories and outcomes. Future studies leveraging adaptive DBS recordings from the basal ganglia (Cascino et al., 2026; Gilron et al., 2021) could directly test how striatal networks relate to the contexts and behavioral states observed in this approach-avoidance navigation task.

It is also important to contextualize the nature of the “threat” in this task. Unlike predator imminence paradigms, which evoke strong defensive responses, the penalty here represents a relatively mild economic threat. Accordingly, the observed neural signals likely reflect evaluation and anticipation of potential danger rather than acute fear responses mediated by structures such as the periaqueductal gray (Mobbs et al., 2007; Roelofs & Dayan, 2022; Signoret-Genest et al.,

2023). This distinction may explain why we observe graded modulation of behavior and neural activity, rather than all-or-none defensive reactions.

Our findings also relate to prior human work on approach–avoidance conflict. For example, human fMRI work has demonstrated that hippocampal BOLD activity scales with threat probability and magnitude, although their effects were closely tied to avoidance behavior (Abivardi et al., 2020). In contrast, our paradigm emphasized strategic navigation amid contextual cues, and revealed dissociable encoding of risk and conflict even when avoidance behavior was relatively infrequent. Similarly, intracranial work reported increased MTL activity during approach in a one-dimensional virtual navigation (Pacman) task (Staveland et al., 2026). Rather than reflecting a discrepancy, these differences may arise from how navigational planning and execution are temporally distributed across the two tasks. In the Pacman task, where movement unfolds along a single dimension with continuous reward acquisition, planning and risk evaluation may update concurrently with approach, leading to elevated MTL activity during movement itself. In contrast, our task separates these processes more clearly: participants are given advance information about trial conditions and often engage in planning during intermission and early stationary periods before initiating movement. As a result, MTL activity in our paradigm may be more prominent during these pre-movement phases, when strategies are formed, rather than during approach execution. Overall, these recent findings provide further credence to the claim that hippocampal and amygdala dynamics flexibly align with the temporal structure of decision-making demands, whether those demands are resolved during movement or beforehand.

Taken together, this study provides novel evidence that human medial temporal lobe activity supports approach-avoidance decision-making in a naturalistic, dynamically evolving

environment, and reveals a functional dissociation between amygdala and hippocampal contributions to this process. Future work should be done to examine functional interactions between the hippocampus and amygdala during approach-avoidance decision-making. Simultaneous recordings from additional nodes in the decision-making network, including prefrontal cortex and striatal regions, will be critical for understanding how flexible, hippocampal-dependent strategies interact with habit-based, reinforcement-driven, or downstream systems. Finally, more targeted behavioral analyses, including complex behavioral transitions and inter-individual interactions, may reveal how neural signals relate to the structure of ongoing decisions. Together, such approaches will elucidate how distributed neural circuits give rise to adaptive behavior in complex, real-world environments.

2.10 Methods

Participants

Nine individuals (ages 25-57; five male, four female) with pharmacoresistant focal epilepsy participated in this study. All participants (Supplementary Table 2.2) had indwelling depth electrodes implanted in the medial temporal lobe (MTL) for clinical purposes. All nine participants had electrode contacts in the hippocampus, and five of them had additional electrode contacts in the amygdala (Figure 2.1B). Electrode placement was determined solely based on clinical criteria, and Brainlab was used to localize electrode contacts. All participants volunteered for the study and provided written informed consent in accordance with a protocol approved by the UCLA Medical Institutional Review Board (IRB #23-001875), and this study was conducted in accordance with the ethical principles for medical research involving human subjects as outlined in the Declaration of Helsinki.

Behavioral Task

Participants performed the approach–avoidance task while freely navigating a large open rectangular space ($\sim 9.6 \times 9.6 \text{ m}^2$; $\sim 31.5 \times 31.5 \text{ ft}^2$) and wearing a Magic Leap 2 augmented reality (AR) headset (Magic Leap, Plantation, FL). The AR platform allowed participants to view the real-world environment in real time while virtual objects and text were superimposed to provide instructions, stimuli, and feedback (Figure 2.1D). Although participants were free to move throughout the room, all task-relevant stimuli were positioned within an invisible circular region of 3 m ($\sim 9 \text{ ft}$) radius. As a result, participant movement during the task was generally localized to this region. The goal of this task was to maximize earnings. Participants could win and lose tokens during each round, and these tokens were converted into monetary compensation at the conclusion of the experiment (2000 tokens = \$1).

Trial Structure

At the start of each trial, a treasure chest appeared within the AR environment. Approaching and reaching the treasure chest resulted in a token reward. At the same time, a moving experimenter was present in the room. If participants approached within 5 ft (~1.5 m) of the experimenter, a token penalty was incurred. Participants were instructed to reach the treasure chest while avoiding proximity to the moving experimenter. Each trial ended when either 1) the participant reached the treasure chest, or 2) the trial time expired (Figure 2.1C).

Trials had a randomly jittered maximum duration of 10–15 seconds, preventing participants from predicting when exactly a trial would end and encouraging timely decisions about whether to pursue the reward. If the participant did not reach the treasure chest before the trial ended, no penalty was incurred; however, the participant forfeited the chance to obtain a reward for that trial. Furthermore, entering the penalty radius did not terminate the trial, allowing participants to incur multiple penalties within a single trial while continuing to attempt to reach the reward.

When participants successfully reached the treasure chest, they received visual and auditory feedback, consisting of an animated reward sequence and an on-screen update indicating the increase in tokens. When participants entered the penalty radius surrounding the experimenter, and the penalty value for that trial was greater than zero, an on-screen notification indicated that a penalty had been incurred.

Trial Conditions and Intermission Period

Reward and penalty magnitudes varied across trials (Supplementary Table 2.1). Before each trial began, participants were placed into an intermission period that displayed the reward and penalty values for the upcoming trial, along with the participant's cumulative score. These values informed the participant of the potential reward and risk associated with the upcoming trial. This

intermission period also allowed them to reposition themselves within the room if desired and control the transition from intermission to trial onset. However, the location of the treasure chest was not visible during intermission. Participants exited intermission and initiated the trial by pressing a button on a handheld controller (Figure 2.1A), upon which the treasure chest became visible (Figure 2.1D).

Experimenter Movement

During the intermission period, the experimenter remained stationary at the center of the room. At trial onset, the experimenter began moving along a programmatically defined trajectory that was randomized across trials. To maintain consistent movement, the experimenter wore a separate Magic Leap 2 headset that displayed a moving visual cue indicating the movement path and speed (experimenter point-of-view shown in Figure 2.1E). This system allowed the experimenter to follow the programmed trajectory while maintaining a constant movement speed of 0.5 m/s, approximating slow walking speed and allowing participants sufficient time to adjust their navigation trajectories as needed.

Importantly, the experimenter could not see the treasure chest, the participant's performance, or when rewards or penalties were incurred. As a result, the experimenter's movement was independent of task events, and the relative positions of the experimenter and treasure chest were not constrained. In some trials, the two could appear in close proximity, whereas in others they were far apart, resulting in natural variability in trial difficulty.

Block Structure

Participants completed multiple 20-trial blocks. Trials were randomly assigned to four trial types with different reward and punishment contingencies (Supplementary Table 2.1). The high-risk, high-conflict, and high-reward conditions were each presented twice as frequently as the

control condition. These trial types were designed to induce different motivational contexts by varying the magnitudes of potential gains and losses. High-risk trials emphasized large potential losses relative to reward, high-reward trials offered large potential gains with minimal penalty, and high-conflict trials presented more balanced reward and penalty values. Control trials provided a baseline condition with reward but no risk of penalty. Again, participants could spend as much time as they wished in the intermission periods before initiating each trial.

Experimental Control and Data Synchronization

Real-time experimental control was implemented with a custom Unity application (Unity Software, San Francisco, CA, version 2022.3.5f1). Behavioral events, including trial onset, trial termination, and proximity collisions, were logged within the Unity framework. Synchronization signals were coordinated by a Raspberry Pi (version 4B) and transmitted to the implanted iEEG acquisition system at the start and end of each recording block, enabling precise temporal alignment between neural recordings, behavioral data, and task events. Additional technical details of the synchronization framework can be found in Topalovic et al. (2020).

The Magic Leap 2 headset (OS Version 1.7.0, Android API Level 29) additionally provided the participant's head position, head rotation, and eye vector tracking data. These measurements were recorded at 30 Hz throughout the experiment. We applied the Magic Leap 2's Custom Fit App for each participant to optimize device fit and gaze calibration for each participant. Magic Leap Lens prescription inserts were used for participants requiring vision correction, as the participants could not wear standard eyeglasses under the augmented reality headset.

Motion Tracking

Participant position was continuously tracked using an OptiTrack motion capture system (NaturalPoint Inc., Corvallis, OR) with Motive software (version 3.0.1). Thirty wall-mounted

high-resolution infrared cameras were distributed throughout the room and tracked a rigid-body marker affixed to the participant's Magic Leap headset. This rigid body marker consisted of multiple reflective spheres attached to the headset and was recorded at 120 Hz with sub-millimeter spatial precision. An additional OptiTrack camera recorded a wide-angle video of the room during the experiment.

In parallel, the Magic Leap 2 headset also provided motion tracking data. However, OptiTrack measurements served as the primary source of positional data for behavioral analyses due to their higher spatial accuracy and reliability. The two motion tracking streams were cross-correlated to validate alignment between datasets.

iEEG Data Acquisition

Intracranial EEG (iEEG) recordings were obtained using the U.S. Food and Drug Administration (FDA)-approved RNS® System (NeuroPace Inc., Mountain View, CA), a device typically used for seizure detection and clinical responsive neurostimulation. To eliminate stimulation artifacts during the experiment, therapeutic stimulation was temporarily disabled with participant informed consent, and the device was used exclusively for neural recording. Each participant had two implanted depth leads, each containing four electrode contacts spaced either 3.5 mm or 10 mm apart (Supplementary Table 2.2). This configuration enabled continuous bipolar iEEG recording from up to four channels per participant, sampled at 250 Hz.

Neural data were transmitted in real time via near-field telemetry using a telemetry Wand positioned over the implanted neurostimulator. The Wand was mounted on a custom backpack worn by the participant (Figure 2.1A), allowing unrestricted movement during recording as previously described (Topalovic et al., 2020). Event markers generated by the Unity/Raspberry Pi

system were transmitted to the neurostimulator at the start and end of each recording block, allowing synchronization of neural and behavioral datasets.

Electrode Localization

High-resolution postoperative computed tomography (CT) scans of the head were acquired for all participants. Electrode contact locations were determined by co-registering each participant's CT scan with their preoperative high-resolution structural magnetic resonance imaging (MRI) scans (T1- and/or T2-weighted) using Brainlab Elements software (Brainlab AG, Munich, Germany). Recording contacts were localized to medial temporal lobe (MTL) structures, including the hippocampus and amygdala (Supplementary Table 2.2). Channels located outside the MTL were excluded from analyses.

Detection of Epileptic Events

Epileptic events, including interictal epileptiform discharges (IEDs), were detected separately within each recording channel using a previously established algorithm (Gelinas et al., 2016) that has been applied in our prior RNS System studies (Gill et al., 2023; Maoz et al., 2023; Seeber et al., 2025; Stangl et al., 2021). Briefly, this method employs a double-thresholding approach based on two criteria (1) the envelope of the unfiltered signal exceeding six standard deviations above baseline, or (2) the envelope of the rectified signal filtered between 15–80 Hz exceeding the same threshold. To capture residual epileptic activity surrounding these events, the binary IED vector (1 for IED, 0 otherwise) was smoothed using a Gaussian filter with a 0.05 s window. Samples with smoothed values above 0.01 were additionally marked as IEDs, effectively excluding a ~250 ms window around each detected IED. Using this method, the data per participant identified as IED-related ranged from 0.4% for participant 8 to 5.8% for participant 7. Participants were intentionally selected for relatively low IED activity based on a prior review of

the RNS System's event log. All participants gave informed consent to disable stimulation during the experiment to eliminate stimulation-related artifacts in the experimental iEEG recordings.

Behavioral Data Analysis

Behavioral metrics were compared across the four conditions (high risk, high reward, high conflict, and control trials) using nonparametric statistical tests. Nonparametric methods were selected over parametric testing due to the sample size ($N_{\text{participants}} = 9$) and potential for deviations from normality. Analyses were performed at the subject level to avoid inflating degrees of freedom due to repeated observations within participants. Subject-level summary values were computed first, resulting in one value per participant per condition. Statistical comparisons across the four conditions were then performed using the Friedman test, a nonparametric replacement to repeated-measures ANOVA appropriate for within-subject designs.

When the Friedman test indicated a significant effect ($p < 0.05$), post hoc pairwise comparisons between conditions were performed using two-tailed Wilcoxon signed-rank tests. Six pairwise comparisons were performed across the four conditions, and the six p-values were corrected for multiple comparisons using the false discovery rate correction procedure (Benjamini & Hochberg, 1995). For these pairwise comparisons, test statistics were additionally expressed and reported as standardized z-values, computed by normalizing the signed-rank statistic relative to the expected mean and variance associated with the null hypothesis.

Group-level summaries were visualized by plotting averaged subject-level values across participants (e.g., Figure 2.2A-D). Error bars represent the standard error of the mean (SEM) across all subjects for that condition. Individual subject data points are overlaid alongside group means to illustrate inter-subject variability.

iEEG Data Analysis

Time–frequency analyses of iEEG data were conducted using the continuous wave transform (CWT; ‘cwt’ function implemented in Matlab), which utilizes analytic Morse wavelets (Lilly & Olhede, 2012). This Morse wavelet transform featured a time-bandwidth product of 250, and wavelet power was computed as the squared magnitude of complex wavelet coefficients. After the CWT was computed, the resulting power estimates were interpolated onto a predefined frequency grid. Frequencies from 1–30 Hz were sampled at 0.25 Hz increments and frequencies from 31–80 Hz at 1 Hz increments. These computations were applied to each 6-8 minute recording block on a sample-by-sample basis, providing high temporal resolution to relate transient neural dynamics with approach-avoidance behaviors and other environmental context.

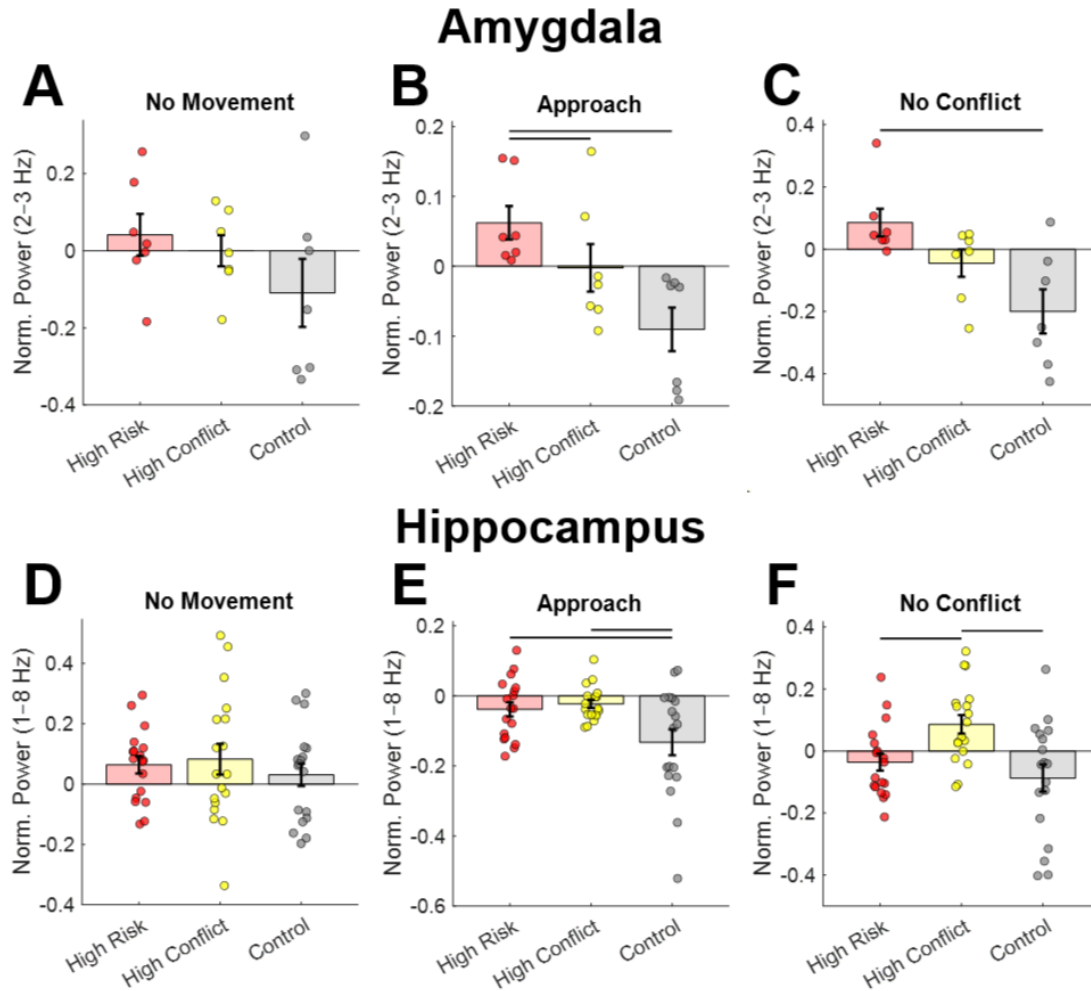
Following CWT wavelet decomposition, band power was calculated by averaging across defined frequency bands (e.g., 1-8 Hz). Power time series were normalized by z-scoring each frequency band within each channel, and across the temporal periods of interest. These normalized time series were aligned with task and behavioral events (e.g., “Intermission”), and average power was computed across the relevant samples (e.g., all intermission-labeled samples). For heatmaps, we visualized oscillatory power across time (4 ms steps) and frequency (1–30 Hz in 0.25 Hz steps, 31–80 Hz in 1 Hz steps).

Data Subsampling and Statistical Testing

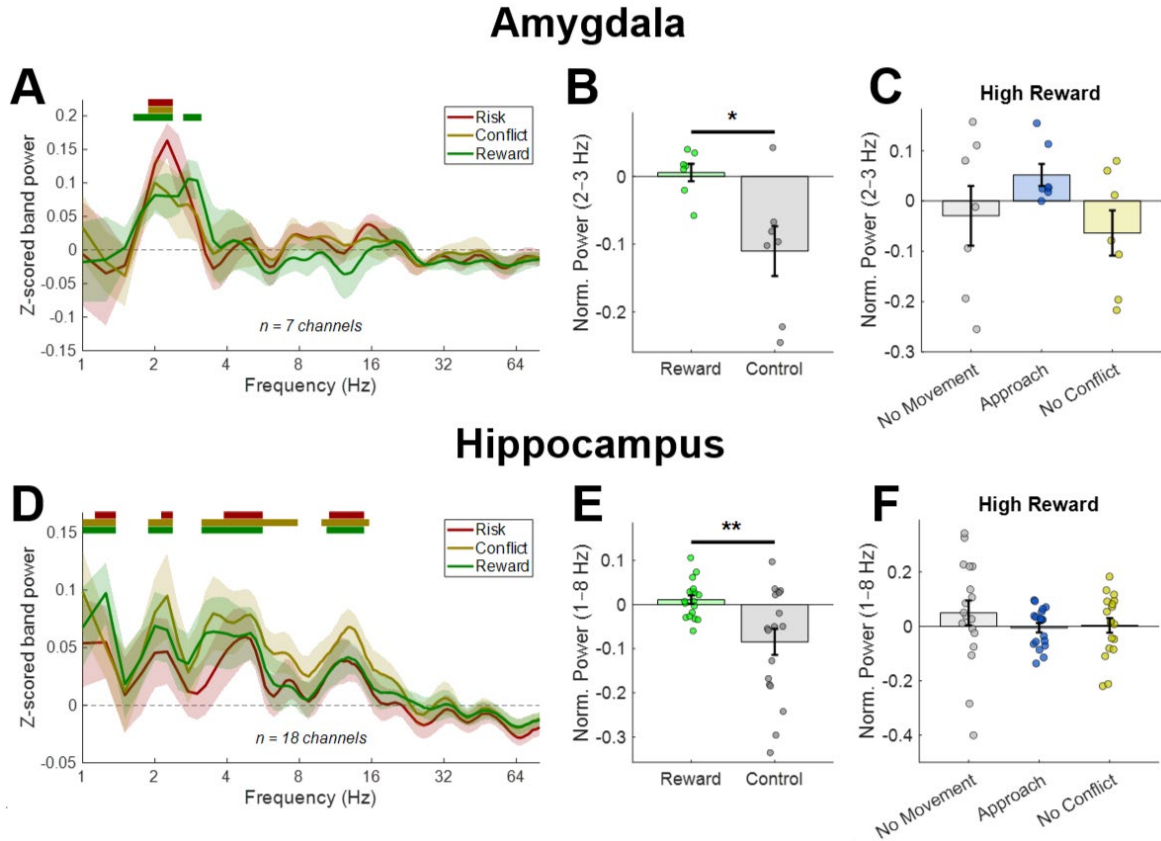
Because participants were unrestricted during the experimental task, it is plausible that they spend more time in one task condition (e.g., high-risk vs. high-reward trial context; Figure 2.2D) which would affect statistical comparisons of band power across these conditions. To ensure balanced comparisons, analyses were performed on 500 iteratively generated, equally sized subsets of data from each condition. For each participant, we first determined the number of samples from

each condition, then subsampled from the conditions with more data to match the smallest condition. Parameters of interest (e.g., CWT-based power estimates) were computed on each matched subset. This procedure was repeated 500 times, and results were averaged across iterations. This subsampling approach was applied consistently across navigation condition comparisons, and all reported statistics and plots on neural data are based on these equal-sized, averaged datasets.

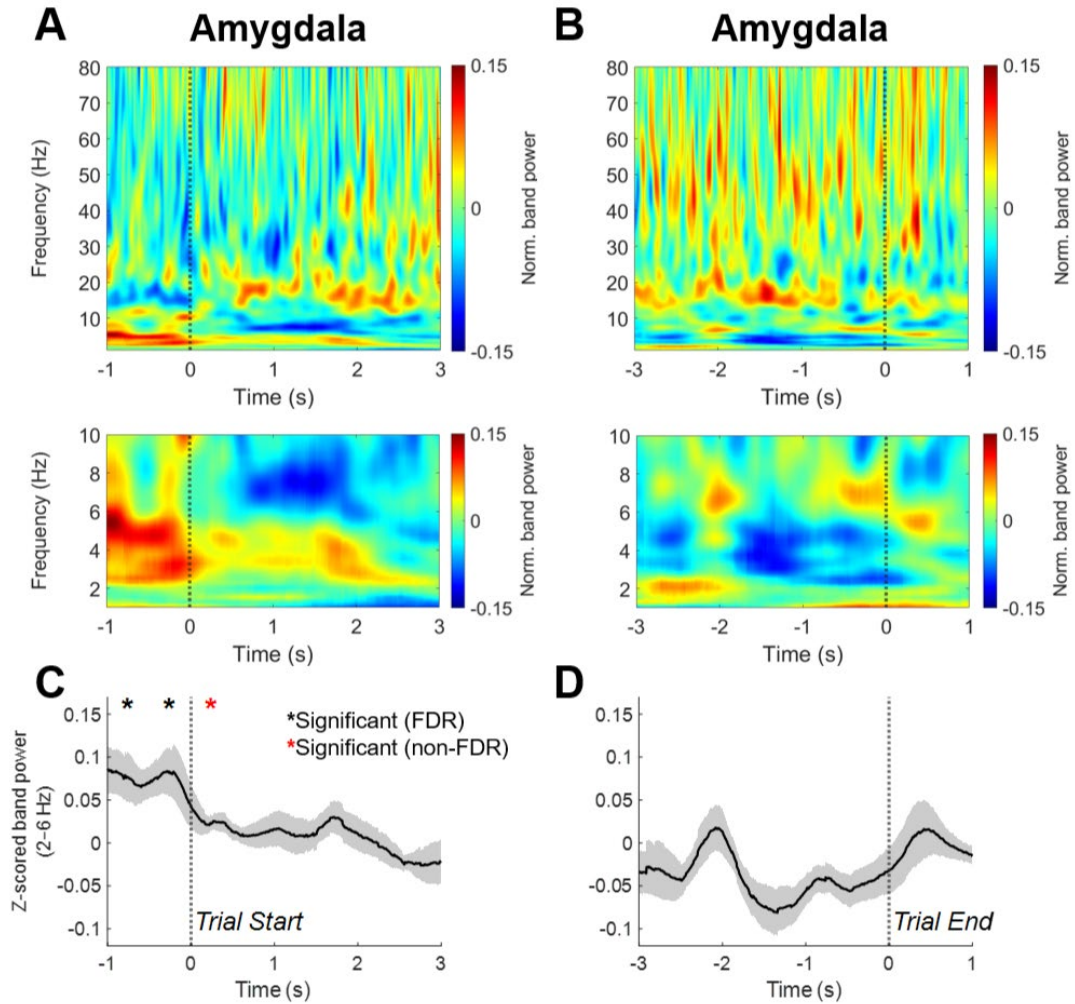
Moreover, statistical testing for channel-level analyses was implemented using the permutation analysis of linear models (PALM) framework (Winkler et al., 2014), which is a nonparametric permutation-based approach for inference within general linear models. In this framework, null distributions are constructed by permuting the data while respecting predefined exchangeability constraints. Electrodes were nested within participants, and therefore permutation exchangeability was restricted within each participant to preserve within-subject dependencies. This approach allows valid inference without assuming independence across electrodes, and thereby reduces the risk of false positive findings. Additionally, for each frequency the condition effect was evaluated using permutation-derived t statistics. Multiple comparisons across conditions were corrected using the false discovery rate (FDR) procedure at each frequency (Benjamini & Hochberg, 1995). One-sided or two-sided tests were applied depending on the presence of a priori directional hypotheses.



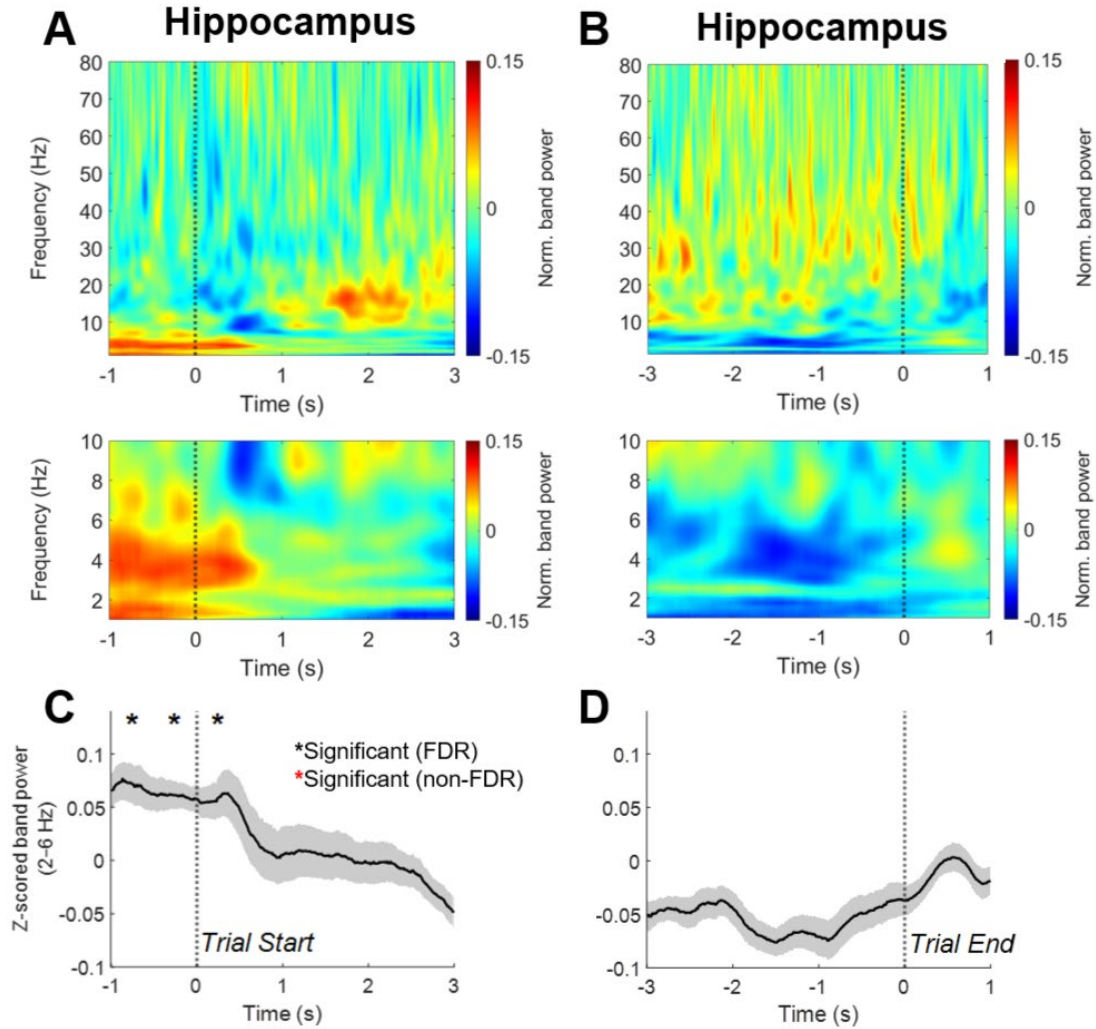
Supplementary Figure 2.1. Trial context encoding across behavioral states. Differences among conditions were tested for each behavioral state separately. (A–C) Amygdala 2–3 Hz activity did not differ across trial conditions during no-movement periods (A), but was elevated in high-risk relative to high-conflict and control during approach (B). Amygdala 2–3 Hz activity was increased in high-risk relative to control during no-conflict behavior (C). (D–F) Hippocampal 1–8 Hz activity did not differ across conditions during no-movement periods (D), but was elevated for high-risk and high-conflict relative to control during approach (E). In the no-conflict behavior, the high-conflict condition was elevated relative to both high-risk and control (F). These results confirm that MTL encoding of trial context is behaviorally selective and most prominent during active navigation to the target. Black lines above bar plots indicate statistically significant differences (FDR corrected; $p < 0.05$).



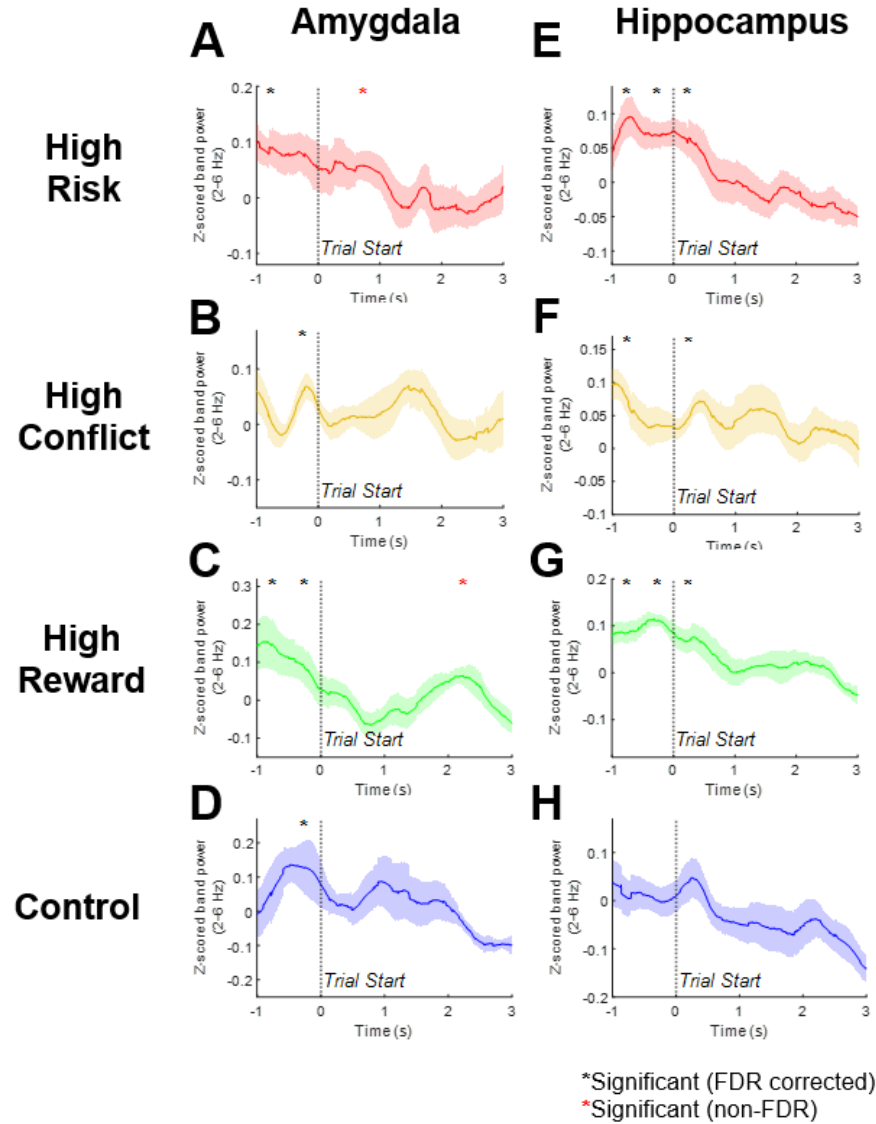
Supplementary Figure 2.2. Amygdala and hippocampus encode high-reward context. (A) Time–frequency analysis revealed increase in low-frequency amygdala power during high-reward relative to control trials, just as for high-risk and high-conflict trials. (B) Within the 2–3 Hz band, amygdala activity was elevated in high-reward compared to control. (C) No differences in amygdala activity were observed across behavioral states within the high-reward condition. (D) Hippocampal activity showed broad low-frequency increases during high-reward trials, just as for high-risk and high-conflict trials. (E) Within the 1–8 Hz band, hippocampal activity was elevated in high-reward relative to control. (F) No behavioral differences were observed within the hippocampus. Altogether, both hippocampus and amygdala encode reward context but do not differentiate behavioral state within this condition. Red, yellow, and green horizontal lines above line charts represent statistically significant differences (FDR corrected) for high risk, high conflict, and high reward trials, respectively. Black lines above bar plots (B,C,E,F) indicate statistically significant differences (FDR corrected; $p < 0.05$). * = $p < 0.05$, ** = $p < 0.01$.



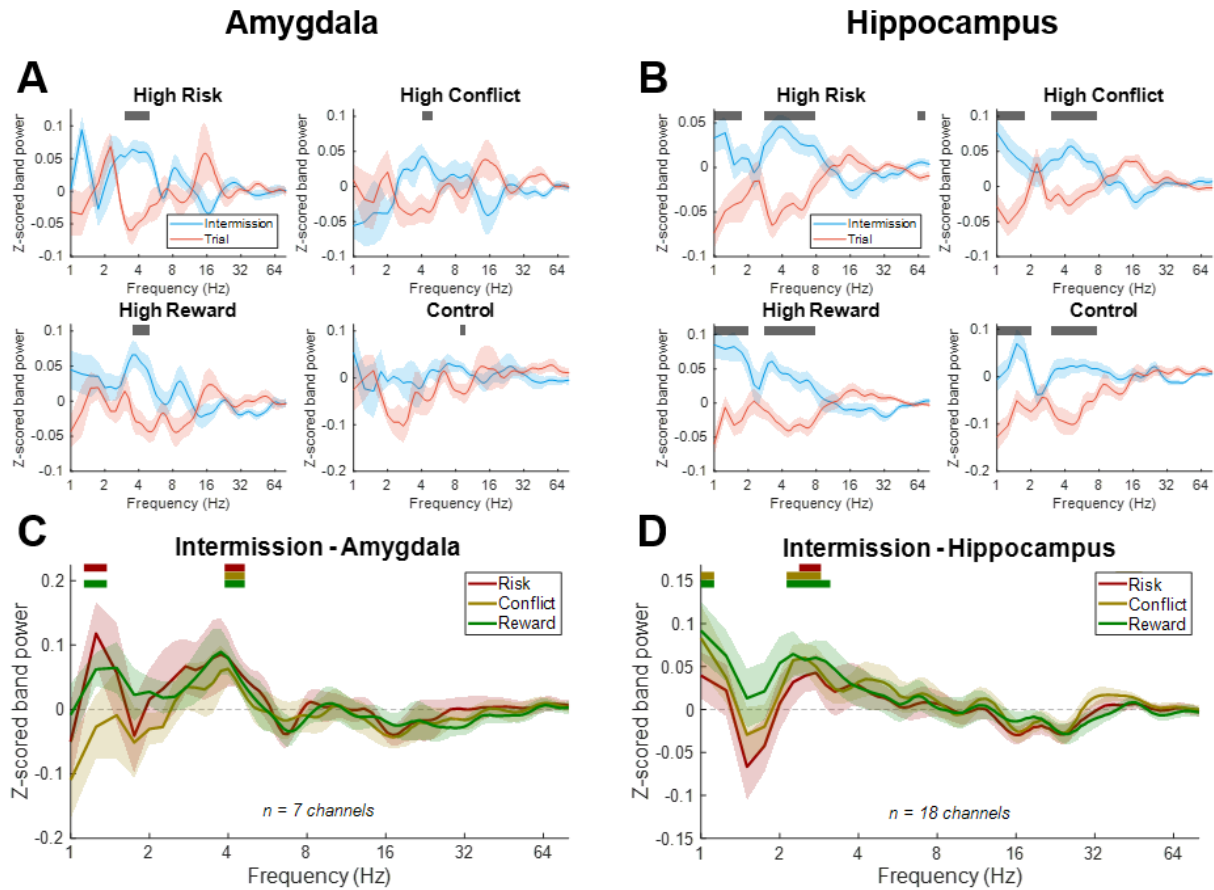
Supplementary Figure 2.3. Amygdala activity is elevated at trial onset. (A) Time-frequency representations aligned to trial onset show elevated low-frequency (~2–6 Hz) amygdala activity prior to and shortly after trial initiation. (B) Alignment to trial offset shows no comparable increase. (C) Quantification of 2–6 Hz power reveals significant pre-trial elevation and a transient, non-significant post-onset increase. (D) No significant modulation was observed around trial offset. This analysis suggests that amygdala activity is enhanced specifically around trial initiation. Black asterisks represent statistically significant elevations (FDR corrected) computed on 0.5 s intervals relative to trial onset and offset. Red asterisks represent elevations that did not survive FDR correction, $* = p < 0.05$.



Supplementary Figure 2.4. Hippocampal activity increases at trial onset. (A) Time-frequency representations aligned to trial onset show elevated low-frequency (~2–6 Hz) hippocampal activity before and shortly after trial initiation. (B) No increase is observed around trial offset. (C) Quantification of the 2–6 Hz band confirms significant pre-trial and early post-onset elevation in hippocampal power. (D) No significant modulation occurs around the end of the trial. These findings parallel amygdala effects in Supplementary Figure 2.3 and indicate increased modulation around trial initiation. Black asterisks represent statistically significant elevations (FDR corrected) computed on 0.5 s intervals relative to trial onset and offset. Red asterisks represent elevations that did not survive FDR correction, $* = p < 0.05$.



Supplementary Figure 2.5. Pre-trial MTL activity across trial contexts. (A–D) Amygdala 2–6 Hz activity was elevated prior to trial onset across all trial types, indicating consistent pre-trial engagement independent of context. (E–H) Hippocampal pre-trial activity was elevated in high-risk, high-conflict, and high-reward conditions, but not in control trials. This suggests that hippocampal pre-trial activity is selectively enhanced in contexts involving potential risk, reward, or approach-avoidance conflict. Black asterisks represent statistically significant elevations (FDR corrected) computed on 0.5 s intervals relative to trial onset and offset. Red asterisks represent elevations that did not survive FDR correction, $* = p < 0.05$.



Supplementary Figure 2.6. Elevated intermission activity across contexts. (A–B) Both the amygdala (A) and hippocampus (B) demonstrate elevated power during intermission compared to active trial periods, particularly in low-frequency bands. **(C)** Amygdala intermission activity varies across upcoming trial types, with low-frequency increases for high-risk, high-conflict, and high-reward conditions relative to control. **(D)** Hippocampal intermission activity similarly differentiates intermission context. Together, these findings indicate that hippocampus and amygdala activity during intermission reflects anticipatory processing and encodes upcoming trial type. Black bars above panels A and B represent statistically significant differences between intermission and trial (FDR corrected, $p < 0.05$). Red, yellow, and green horizontal lines above panels C and D represent statistically significant differences (FDR corrected, $p < 0.05$) for high risk, high conflict, and high reward trials, respectively.

	Reward (Chest)	Punishment (Collision)	P1	P2	P3	P4	P5	P6	P7	P8	P9
High Risk	100	2000	49	79	70	61	43	21	70	66	39
High Conflict	300	500	47	85	61	51	48	28	65	66	35
High Reward	1000	100	48	85	63	46	45	26	63	62	38
Control	500	0	23	39	28	28	23	14	33	33	20

Supplementary Table 2.1. Trial Types. Four trial types (listed in leftmost column) were presented in random order, each associated with different reward and punishment values. The high-risk, high-conflict, and high-reward conditions were each presented twice as frequently as the control condition. The number of trials for each trial type is provided for each participant (P1-P9).

Subject	Age	Channel 1	Channel 2	Channel 3	Channel 4
1 (F)	57	Left HPC	Left HPC	Left AMG	Left HPC
2 (M)	30	Left AMG	Left HPC	Right AMG	Right HPC
3 (F)	32	Left HPC	Left HPC	Right HPC	Right HPC
4 (M)	40	Left HPC	Left HPC	Right AMG	Right HPC
5 (F)	25	Left HPC	Other MTL	Right AMG	Other MTL
6 (F)	46	Left HPC	Other MTL	Other MTL	Other MTL
7 (M)	26	Other MTL	Not in MTL	Left HPC	Not in MTL
8 (M)	26	Other MTL	Other MTL	Right HPC	Right HPC
9 (M)	41	Left AMG	Left HPC	Other MTL	Right AMG

Supplementary Table 2.2. Channel localization across participants. Localization of each bipolar recording channel, based on the anatomical positions of its two contacts (+/-). Channels were assigned to a region of interest only if both contacts were located within or along the border of that region (hippocampus or amygdala). All nine participants had hippocampal contacts, and five participants had additional amygdala contacts. Bolded channels were included in the analysis. In total, 18 hippocampal channels were analyzed (12 left hemisphere, 6 right hemisphere) and 7 amygdala channels (3 left hemisphere, 4 right hemisphere). HPP: hippocampus; AMG: amygdala, MTL: medial temporal lobe.

Conclusion

Across the two studies presented in this dissertation, a central theme emerges: advances in ambulatory intracranial recording technologies now make it possible to study human neural dynamics during real-world behavior, rather than relying on artificial or highly constrained paradigms (Stangl et al., 2023; Topalovic et al., 2020). This shift is particularly significant for understanding human theta oscillations, whose functional role has remained elusive despite decades of study. By embedding neural recordings within reality-based naturalistic tasks, ranging from memory-guided navigation to approach-avoidance decision-making, these experiments demonstrate that theta activity cannot be attributed to any single cognitive variable. Rather, theta reflects nonlinear interactions between multiple behavioral and contextual factors, including movement, eye behavior, spatial memory demands, and motivational context.

For example, eye movements enhanced theta selectively during memory-guided navigation, and this effect was strongest during planning periods (Zubair et al., 2026). Similarly, hippocampal theta increased during navigational planning periods, but specifically under conditions of impending approach-avoidance conflict, suggesting that hippocampal theta reflects context-dependent evaluation rather than simple navigational planning. Movement, in turn, appeared to amplify underlying neural representations, potentially through increased sensorimotor coupling or environmental sampling, thereby revealing differences among behavioral contexts (Bush et al., 2017; Siegel et al., 2012). Together, these findings argue against studying cognitive variables in isolation and instead support an approach centered on behavioral motifs, in which complex, ecologically valid behaviors are decomposed into recurring, structured patterns (Mobbs et al., 2021). Such an approach preserves external validity while allowing mechanistic insight into how neural signals map onto real-world cognition.

A key question that follows is why theta oscillations warrant such attention. Converging evidence suggests that theta activity is not only central to medial temporal lobe function, including memory, navigation, and decision-making, but is also disrupted across a range of neurological and psychiatric disorders. In Alzheimer's disease, for instance, resting-state EEG studies consistently report elevated low-frequency power, including theta, alongside reductions in higher-frequency activity (Benwell et al., 2020; Musaeus et al., 2018). At the same time, task-related theta modulation is often diminished, indicating a failure to appropriately recruit theta dynamics during cognitive demand (Goodman et al., 2019). Disruptions in theta-band coherence further suggest impaired large-scale network coordination (Fide et al., 2023). Similar alterations in theta and related circuits have been implicated in disorders of approach-avoidance behavior, including anxiety and addiction (Adhikari, 2014; Bach et al., 2019b; Harper et al., 2018; McNaughton & Corr, 2004).

Much of the aforementioned work relies on surface EEG, which provides limited access to medial temporal lobe structures, regions that are both early targets of Alzheimer's pathology and critical for spatial navigation and memory-guided behavior. Moreover, traditional laboratory tasks sometimes fail to capture the complexity of real-world navigation, where impairments are most apparent. Indeed, patients with Alzheimer's disease show pronounced deficits during active navigation tasks that require planning, updating, and prospective decision-making, such as the Floor Maze Test (Bhasin et al., 2023; Levine et al., 2020; Parizkova et al., 2018; Plácido et al., 2022). Given the established role of hippocampal theta in spatial navigation and active information sampling, disruptions in theta dynamics may directly contribute to these real-world deficits. A more precise, behaviorally grounded understanding of theta is therefore essential for linking neural dysfunction to everyday cognitive impairment.

Ultimately, this line of work points toward the development of theta-based biomarkers of cognitive function. Rather than treating theta as a static feature measured at rest, recent findings suggest that its functional relevance lies in how theta dynamically engages during specific behaviors. This raises the possibility of identifying everyday activities or behavioral contexts that reliably enhance or suppress theta, with potential applications for cognitive training and rehabilitation. In parallel, theta dynamics could serve as a physiological readout for evaluating emerging treatments, including pharmacological, genetic, or neuromodulatory interventions. For instance, monitoring task-related theta during naturalistic behavior could provide a more sensitive measure of treatment efficacy than traditional neuropsychological testing alone.

These considerations are particularly relevant for the eventual development of closed-loop neuromodulation therapies. While prior attempts to treat Alzheimer's disease using deep brain stimulation have shown limited success (Leoutsakos et al., 2018; Lozano et al., 2016), such approaches have largely relied on open-loop stimulation that is not informed by ongoing neural dynamics. A more effective strategy may involve aligning stimulation with endogenous theta activity, regarding both phase and timing. Evidence suggests that different phases of theta oscillations support distinct computational processes, including encoding and retrieval (e.g., the SPEAR model), and that memory performance can fluctuate rhythmically at theta frequencies (Biba et al., 2026; Buzsáki, 2002; Hasselmo et al., 2002). These findings highlight the importance of understanding not only when theta is active, but what it represents and how it evolves over time.

The findings outlined in this dissertation emphasize that any attempt to modulate hippocampal function must consider its broader role beyond memory. As highlighted in Chapter 2, hippocampal theta is involved in evaluating approach-avoidance conflict and guiding decision-making under uncertainty. Interventions that indiscriminately enhance hippocampal activity may

therefore carry unintended consequences, such as altering risk sensitivity, increasing avoidance, or promoting maladaptive behaviors. This underscores the need for a balanced, circuit-level understanding of hippocampal function, in which memory, emotion, and decision-making are viewed as interdependent processes rather than isolated domains.

Finally, these findings contribute to a broader shift in neuroscience toward studying cognition in naturalistic settings. By combining intracranial recordings with immersive behavioral paradigms, this work bridges the gap between controlled experiments and real-world behavior, providing new insight into how neural circuits operate during everyday decision-making. Beyond clinical applications, this approach has the potential to advance our understanding of spatial cognition, social behavior, and adaptive decision-making, and to establish a foundation for future studies that integrate multiple brain regions and analytical approaches. In addition, leveraging adaptive neurostimulation platforms to perturb these circuits during behavior could provide causal insight into the role of theta dynamics in cognition. Altogether, such efforts will help move the field toward a mechanistic understanding of how neural oscillations support real-world behavior, and how these processes can be harnessed to improve human health.

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