Role of the Head Direction Signal in Memory Replay

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Table of Contents

Abstract

During sleep, spontaneous neuronal activity in the spatial navigation system recapitulates previous wake experiences, and this phenomenon is instrumental for learning and memory. Specifically, in the hippocampus, CA1 place cell ensembles are spontaneously replayed in sequences corresponding to trajectories of the animal in previously visited environments. In parallel, head-direction (HD) cells of the anterodorsal thalamic nucleus (ADn), which fire for a specific direction of the animal's head, remain coordinated during sleep. CA1 place cells and ADn-HD cells are both essential for spatial navigation and memory. However, it is still unclear if and how the activity of thalamic HD cells and hippocampal place cells is synchronized during sleep, and whether this coordination is influenced by prior learning experiences. To address this question, we recorded neuronal ensembles of ADn-HD cells and CA1place cells in freely moving mice performing a spatial memory task. Specifically, animals were trained in a forced alternation task on a Y-maze, during which they had only one path to take on each trial. On the day of the recording, after the forced choice task, the animal performed a free alternation task in which it was free to choose either one of the two arms, and then spontaneously alternate between them. Sleep was recorded in the home cage before and after each task. We found that HD cells fired systematically 50-100 ms before hippocampal neurons during sleep, regardless of the sleep session. Additionally, there was no reactivation observed in the hippocampus during the two sleep sessions after the tasks, as expected in a highly familiar environment. ADn-HD cells showed no reactivation after the forced alternation but interestingly, showed strong reactivation after the free alternation task. We then assessed the coordinated reactivation of CA1 place cells and ADn-HD cell ensembles. Notably, we detected a synchronized reactivation of ADn-HD and CA1 place cell groups during sleep exclusively following the free alternation task. Furthermore, our decoding analysis revealed that during non-REM sleep, the HD selectively visits specific angles related

to the task. In conclusion, the co-firing of thalamic HD cells is modified with learning and is reflected in subsequent sleep activity. As HD tuning was preserved across tasks, these results suggest that learning-specific information is thus encoded independent of the HD signal. Although ADn activity always precedes CA1 spiking, learning would strengthen the coordination of anterior thalamic cells and hippocampal neurons that were activated during wake experience. These results suggest that the organization of the HD system, believed to be governed by low-dimensional attractor dynamics, can be modified by spatial learning.

Résumé

Pendant le sommeil, l'activité neuronale spontanée dans le système de navigation spatiale récapitule les expériences vécues pendant l'éveil, et ce phénomène est essentiel pour l'apprentissage et la mémoire. En particulier, dans l'hippocampe, les ensembles de cellules de lieu CA1 sont rejoués spontanément en séquences correspondant aux trajectoires de l'animal dans des environnements préalablement visités. En parallèle, les cellules de direction de la tête (HD) du noyau antérodorsal du thalamus (ADn), qui s'activent pour une direction spécifique de la tête de l'animal, restent coordonnées pendant le sommeil. Les cellules de lieu CA1 et les cellules HD de l'ADn sont toutes deux essentielles pour la navigation spatiale et la mémoire. Cependant, il n'est pas encore clair **si** et comment l'activité des cellules HD thalamiques et des cellules de lieu hippocampiques **est** synchronisée pendant le sommeil, et si cette coordination est influencée par des expériences d'apprentissage antérieures. Pour répondre à cette question, nous avons enregistré des ensembles neuronaux de cellules HD de l'ADn et de cellules de lieu CA1 chez des souris en mouvement libre effectuant une tâche de mémoire spatiale. Les animaux ont été entraînés à une tâche d'alternance forcée sur un labyrinthe en Y, dans lequel ils n'avaient qu'un seul chemin à emprunter à chaque essai. Le jour de l'enregistrement, après la tâche de choix forcé, l'animal a réalisé une tâche d'alternance libre où il était libre de choisir l'un des deux bras, puis d'alterner spontanément entre eux. Le sommeil a été enregistré dans la cage d'habitation avant et après chaque tâche. Nous avons **observé** que les cellules HD s'activaient systématiquement 50 à 100 ms avant les neurones hippocampiques pendant le sommeil, indépendamment de la session de sommeil. De plus, il n'y avait aucune réactivation observée dans l'hippocampe lors des deux sessions de sommeil après les tâches, comme prévu dans un environnement hautement familier. Les cellules HD de l'ADn n'ont montré aucune réactivation après l'alternance forcée, mais ont, de manière intéressante, montré une forte réactivation après la tâche d'alternance libre. Nous avons

ensuite évalué la réactivation coordonnée des cellules de lieu CA1 et des ensembles de cellules HD de l'ADn. Notamment, nous avons détecté une réactivation synchronisée des groupes de cellules HD de l'ADn et de cellules de lieu CA1 pendant le sommeil uniquement après la tâche d'alternance libre. En outre, notre analyse de décodage a révélé que pendant le sommeil non-REM, les cellules HD visitaient sélectivement des angles spécifiques liés à la tâche. En conclusion, la co-activation des cellules HD thalamiques est modifiée par l'apprentissage et se reflète dans l'activité du sommeil subséquente. Étant donné que le réglage des cellules HD a été préservé à travers les tâches, ces résultats suggèrent que l'information spécifique à l'apprentissage est ainsi encodée indépendamment du signal HD. Bien que l'activité de l'ADn précède toujours le déclenchement des cellules CA1, l'apprentissage renforcerait la coordination des cellules thalamiques antérieures et des neurones hippocampiques qui ont été activés lors de l'expérience d'éveil. Ces résultats suggèrent que l'organisation du système HD, qui serait gouvernée par des dynamiques d'attracteur de faible dimension, peut être modifiée par l'apprentissage spatial.

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And last but certainly not least, I'd like to quote the words of Snoop Dogg: " I want to thank me for believing in me, I want to thank me for doing all this hard work. I wanna thank me for having no days off. I wanna thank me for never quitting. I wanna thank me for always being a giver and trying to give more than I receive. I wanna thank me for trying to do more right than wrong. I wanna thank me for being me at all times."

Contribution to original knowledge

In this thesis we explored the relationship between thalamic HD cells and hippocampal place cells during non-REM sleep, in the context of learning .To this end, we conducted recordings of neuronal activity in mice performing spatial memory tasks. The key highlights of our work that represent novel contributions to the field are as follows:

- Neural Synchronization during Sleep: We described the interaction and coordination between ADn-HD cells and CA1 place cells during non-REM sleep, before and after learning. This provides new insights into how the brain integrates spatial location with directional orientation to form a coherent representation of the environment during sleep.

- Differential Reactivation Patterns: We identified coordinated reactivation patterns of CA1 place cells in the hippocampus and ADn-HD cells during non-REM sleep, contributing to the understanding of neural replay processes integral to spatial memory formation. Additionally, we introduced the novel observation of ADn-HD cell reactivation during non-REM sleep following spatial learning.

- Decoding Spatial Stability: By reconstructing head direction and employing both Bayesian, linear decoding, and isomap projection, we unveiled the neural consistency across wakefulness and non-REM sleep. This highlights the head direction system capacity to consistently encode spatial representations across different brain states and task complexities.

- The head direction system no longer appears to function as a continuous attractor network: Our results indicate that during non-REM sleep, the head direction (HD) signal deviates from the continuous attractor model, which assumes a stable neural representation for all head orientations. Instead, the HD signal shows a tendency to focus on specific task-related angles, revealing a directional preference or bias.

Contribution of Authors

Sandybel Angeles-Duran authored the thesis and conducted all experimental procedures, including surgeries, recordings, and animal training. Adrien Peyrache contributed through manuscript revisions and editing and worked alongside Sandybel on both experimental design and data analysis.

List of Figures

List of abbreviations

ADn - Anterodorsal Nucleus

CA1 - Cornu Ammonis 1

CA3 - Cornu Ammonis 3

DG - Dentate Gyrus

DTN - Dorsal Tegmental Nucleus

EC - Entorhinal Cortex

EMG - Electromyography

EV - Explained Variance

HD - Head Direction

Isomap - Isometric Mapping

LFP - Local Field Potential

LMN - Lateral Mammillary Nucleus

mPFC - Medial Prefrontal Cortex

MVN - Medial Vestibular Nucleus

non-REM - non-Rapid Eye Movement

PoS - Postsubiculum

REM - Rapid Eye Movement

RSC - Retrosplenial Cortex

REV - Reversed Explained Variance

SEM - Standard Error of the Mean

SWRs - Sharp-Wave Ripples

SWS - Slow Wave Sleep

1. Introduction

In the realm of neuroscience, a fascinating yet complex process occurs during the quietude of sleep — the consolidation of memories. This brain phenomenon is more than just rest; it includes a complex series of neural processes. Particularly during non-rapid eye movement (non-REM) sleep, the brain is actively engaged in replaying the experiences and learnings of the waking state. This phenomenon, pivotal for memory retention and learning, opens a window into understanding the intricate mechanisms of the human brain (Diekelmann & Born, 2010).

Pioneering studies in the field of neuroscience have long established the critical role of sleep on memory consolidation. The phenomenon of 'sleep replay,' especially in the hippocampal CA1 region, has been a subject of fascination and extensive investigation (Skaggs & McNaughton, 1996; Wilson & McNaughton, 1994). This phenomenon involves the reactivation of hippocampal place cells, which are known to encode spatial information, during non-REM sleep phases. Complementing this is the intriguing role of the anterodorsal nucleus of the thalamus (ADn) and head direction (HD) cells, both during wakefulness and non-REM sleep (Sargolini et al., 2006; Taube, 1998). It has been described that HD cells of the ADn, which fire for a specific direction of the animal’s head, remain coordinated during sleep (Peyrache et al., 2015). The intricate relationship between these neural elements, especially during sharp wave ripples (SWRs) associated with memory replay, forms the foundation of our understanding of memory's neural basis (Buzsáki, 1989)

Despite significant advancements in the field, a fundamental gap remains in our understanding of how thalamic HD cells and hippocampal activity are coordinated during sleep and how this coordination is influenced by learning. The HD signal is crucial for spatial

navigation, and the anterior thalamus is essential for spatial memory (Aggleton & O'Mara, 2022; Goodridge & Taube, 1997; Winter et al., 2015).

Yet, whether thalamic HD cells and hippocampal activity are coordinated during sleep and how much this coordination depends on learning remain largely unexplored territories. This thesis poses the pivotal question: Does the ADn-HD signal contribute to the replay of spatial trajectories encoded by CA1 place cells during sleep?

The aim of this study is to explore the coordination between ADn-HD cells and hippocampal place cells during sleep, acknowledging the critical role of the HD signal in spatial navigation and the anterior thalamus in spatial memory, as well as the essential contribution of CA1 place cells to spatial navigation. The intricacies of how thalamic HD cells and hippocampal activity synchronize during sleep and the degree to which this coordination is modulated by learning experiences are yet to be fully understood. Our hypothesis posits that there will be a coherent interaction between HD cells in the ADn and CA1 place cells during sleep, indicative of synchronized neural activity crucial for memory consolidation. This interaction is expected to be modulated by prior learning, highlighting the integrated roles these regions play in the consolidation of spatial memories during sleep. To address this question, we recorded neuronal ensembles of ADn-HD cells and CA1 hippocampal place cells in freely moving mice performing a spatial memory task. Specifically, animals were trained on a forced alternation task on a Y-maze, limiting them to one path on each trial. Subsequently, during the free alternation task, the animals had the freedom to choose between two arms, allowing for spontaneous alternation. Sleep was recorded in the home cage before and after each task. Our observations revealed that HD cells fired systematically 50-100 ms before hippocampal neurons, independent of the sleep session (Viejo & Peyrache, 2020). In the post-task sleep sessions, CA1 place cell reactivation was no observed, aligning with the expectation that reactivation decreases as novel environments

become familiar (Cheng & Frank, 2008). In contrast, a robust reactivation of ADn-HD cells was exclusively observed after the free alternation task, with no such reactivation noted following the forced alternation task. Next, we assessed the coordinated reactivation of CA1 place cells and ADn-HD cells. We found a significant synchronized reactivation of the ADn-HD and CA1 place cell ensembles during sleep following the free alternation task. This highlights the influence of task complexity on the neural dynamics during subsequent sleep periods.

Decoding techniques, such as Bayesian and linear decoding, showed that during non-REM sleep, the decoded angles are not evenly distributed; instead, certain angles corresponding to the Y-maze are revisited more frequently. This indicates that the HD signal during non-REM sleep deviates from the continuous attractor model, where neural representation of head direction is expected to be uniform across all orientations. Instead, our findings highlight that the HD signal during non-REM sleep is biased towards specific task-related angles, suggesting a preference for certain directions.

In summary, while ADn activity consistently precedes CA1 spiking, spatial learning enhances the coordination between anterior thalamic cells and hippocampal neurons activated during the spatial memory task. Learning also modifies how ADn-HD cells co-fire, a change evident in their activity during subsequent sleep. Despite this, the tuning of HD cells remains consistent across different tasks, indicating that learning-specific information is encoded separately from the HD signal. Furthermore, our findings reveal that during non-REM sleep, the HD signal shifts away from the expected continuous attractor model, where head direction is uniformly represented across all possible orientations. Instead, there is a preference for specific angles related to the learned task, suggesting the HD signal is biased towards certain directions.

2. Literature review

2.1.Memory formation and consolidation

The process of memory formation and consolidation is a cornerstone in the field of cognitive neuroscience, shaping our understanding of how experiences are encoded, stored, and retrieved within the human brain. This section of the literature review explores the foundational concepts and theories that underpin our current understanding of these processes.

After the initial encoding of new information, memory exists in a vulnerable state known as short-term memory, characterized by its susceptibility to disruption (Nader et al., 2000). This phase of memory, although crucial for immediate recall, lacks the stability found in more established memory states. Short-term memory serves as a transitory phase, where information is either forgotten or gradually transformed into a more durable form, known as long-term memory. The transformation of memory from a labile to a stable state is termed "consolidation," a concept first introduced by Müller and Pilzecker. Consolidation describes the process through which memories become stabilized over time, a process inherently linked to learning and neural plasticity (Lechner et al., 1999). This transformation is not merely a passive transition but involves active neural reorganization and strengthening of memory traces (Figure 1).

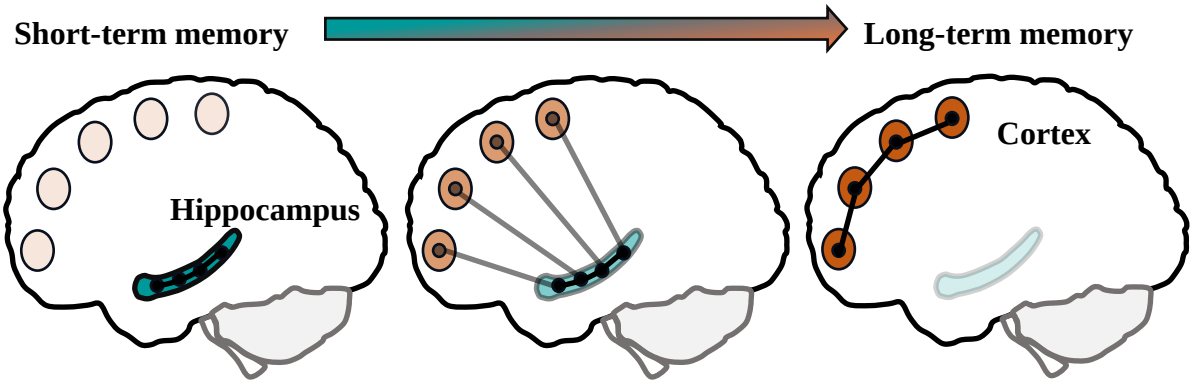

Figure 1 The memory consolidation theory. It posits that while the hippocampus is initially crucial for forming new memories, over time these memories transition to become more reliant on the cortex, reflecting a process where they are gradually integrated and stabilized within the cortical structures.

A pivotal theory in memory research is the "system consolidation theory", which posits that new declarative memories initially depend on the hippocampus but gradually become independent of this structure as they are integrated into neocortical networks (Dudai, 2004; Frankland & Bontempi, 2005). This theory aligns with the well-documented role of the hippocampus in the formation of new memories and its subsequent diminishing involvement as memories are transferred and assimilated into long-term storage in the neocortex (Nader et al., 2000).

The critical role of the hippocampus in recent memory formation has been further substantiated by studies on memory impairment. Penfield, Milner, and Scoville's work with patients who had lesions in the medial temporal lobe provided concrete evidence that damage to the hippocampus impairs recently acquired memories while sparing older, more established memories (Scoville & Milner, 1957). In contrast, damage to the neocortex has been shown to impair remote memories, indicating the distinct roles of these brain regions in memory consolidation (Bayley et al., 2003).

David Marr was among the first to propose a model of systems consolidation, suggesting that information in the hippocampus is eventually transferred to the neocortex for long-term storage (Dash et al., 2004; Graham & Hodges, 1997). Marr's model posited that the encoding of a memory trace after an experience, and its subsequent transfer from the hippocampus to the cortex, relies on the replay of waking patterns during offline states, such as sleep or rest (Marr, 1970, 1971). This model highlights the dynamic nature of memory,

where the initial encoding is only the beginning of a complex journey of transformation and integration within the brain's neural networks.

2.2.Memory Consolidation During Sleep

In the vast landscape of neuroscience, the study of memory consolidation during sleep has emerged as a critical area of inquiry. Over the past several decades, a burgeoning body of evidence has reinforced the concept that sleep significantly promotes the consolidation of newly acquired memories (Diekelmann & Born, 2010; Jenkins & Dallenbach, 1924; Maquet, 2001).

Sleep, a complex and cyclic physiological process, is composed of distinct stages that can be broadly categorized into rapid eye movement (REM) and non-rapid eye movement (non-REM) phases. Each cycle of sleep, typically lasting about 90 minutes, is a progression through these various stages, each characterized by unique patterns of brain activity and physiological functions. Non-REM divided into three stages N1-N3. Stage 1 marks the transition from wakefulness to sleep. It is a light sleep phase during which the body begins to relax, characterized by slow eye movements and reduced muscle activity. Brain waves in this stage show a reduction in frequency, with the presence of theta waves (Carskadon & Dement, 2011). As sleep deepens, stage 2 of non-REM sleep is entered. This stage is marked by the cessation of eye movement and a further decrease in muscle activity. The brain begins to produce sleep spindles and K-complexes, indicative of a deeper level of relaxation and disengagement from the surroundings (De Gennaro & Ferrara, 2003). Stage 3, often referred to as deep sleep, is characterized by the prevalence of slow wave sleep (SWS). This stage features delta waves, which are high amplitude, low-frequency brain waves. SWS is crucial for restorative processes and plays a significant role in memory consolidation and physical recovery (Steriade, 2006). In contrast, REM sleep is marked by ponto-geniculo-occipital

(PGO) waves and theta activity (4-8 Hz) (Buzsáki, 2002). Both REM and non-REM sleep phases play integral roles in the consolidation of different types of memory. Behavioral research has consistently shown that sleep following learning activities enhances the retention of both declarative memories, which include facts and events, and procedural memories, which encompass skills (Marshall & Born, 2007; Robertson et al., 2004; C. Smith, 2001).

The consolidation of memories during sleep is believed to involve a dynamic dialogue between the hippocampus and cortical regions, a process crucial for the long-term storage of memories (McClelland et al., 1995). This dialogue is characterized by the interplay between hippocampal sharp-wave ripples, cortical delta waves, and thalamo-cortical spindles, which collectively facilitate the reorganization of prefrontal cortical networks during offline states (Maingret et al., 2016; Peyrache et al., 2011; Siapas & Wilson, 1998; Sirota et al., 2003). These neural interactions are pivotal in transferring and transforming memory traces from a hippocampus-dependent state to a more distributed representation within the neocortical networks.

One of the most significant observations in the field of sleep research is the reactivation of learning-related neuronal firing patterns in the hippocampus and medial prefrontal cortex (mPFC) during subsequent SWS periods following learning. This reactivation suggests a physiological mechanism that underlies memory consolidation during sleep (Peyrache et al., 2009). Such reactivation is not a mere repetition of neural activity; instead, it represents a process of reinforcement and integration of memory traces, essential for transforming transient experiences into lasting memories. This intricate process of memory consolidation during sleep not only highlights the complexity of cognitive processes during seemingly quiescent states but also underscores the critical function of sleep on memory formation, stabilization, and long-term retention. As research continues to unravel the nuances of these processes, our understanding of the neural basis of memory consolidation

becomes increasingly refined, offering profound insights into the fundamental workings of the human brain.

2.3. The navigation system in the brain

The navigation system within the brain is underpinned by a network of specialized regions working in concert. Central to this system, the hippocampus plays a pivotal role in forming and retrieving spatial memories, primarily through its place cells (O'Keefe & Nadel, 1978). These cells create a mental representation of the environment, fundamental to navigation and memory. Adjacent to the hippocampus, the entorhinal cortex, with its grid cells, complements this navigation system by providing a structured spatial metric, crucial for accurate spatial navigation and memory consolidation (Hafting et al., 2005). Head direction cells, mainly located in the thalamus and presubiculum, offer a compass-like function, essential for orienting oneself in space (Taube, 1998). The parietal cortex enhances this system through path integration, integrating sensory inputs to construct a coherent spatial orientation (McNaughton et al., 2006). The integration of these elements is vital for navigating complex environments, forming the foundation of spatial memory, and is integral to various cognitive processes including planning and decision-making. This sophisticated network underscores the importance of navigation not only as a means of physical orientation but also as a key component in the broader scope of cognitive functions, influencing how we interact with, remember, and understand the world around us.

2.3.1 The sense of position: hippocampal place cells

Since O'Keefe & Dostrovsky's groundbreaking discovery of place cells in the hippocampus in 1971, research into the neural representation of spatial environments has advanced significantly. Place cells, primarily located in the hippocampal CA1 and CA3 regions, are

unique neurons that exhibit increased firing rates when an animal occupies a specific location within its environment, termed as place field (Figure 2) (O'Keefe & Dostrovsky, 1971; Wilson & McNaughton, 1993). These cells are instrumental in providing spatial position information, forming the basis of what is often referred to as a "cognitive map," a mental representation of the spatial layout of the environment.

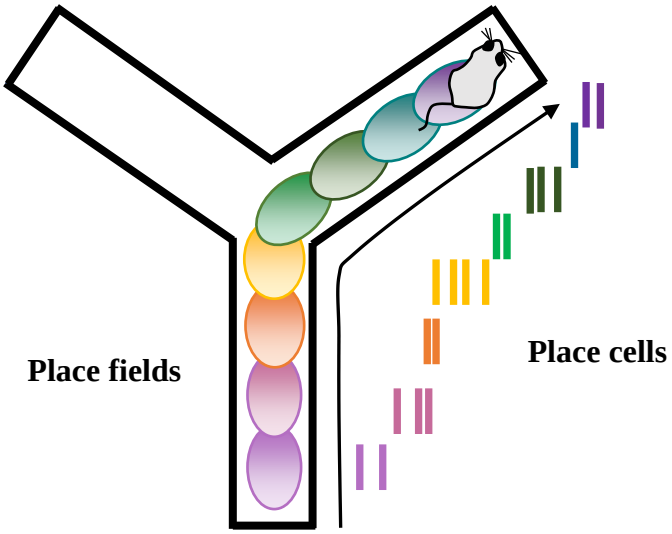

Figure 2 Hippocampal place cells. Activity of place cells, with each row of colored tick marks denoting the spikes from a single cell. As the rat moves through its environment during wakefulness, these place cells fire in a sequential order that maps to distinct spatial regions, known as place fields.

The functionality of place cells is notably multimodal. They integrate information from various sensory inputs, such as visual, auditory, and olfactory cues, to localize their firing to specific regions, adapting to the complexities of different environments (Jeffery, 2007). This multimodal nature allows for a rich and accurate representation of space, crucial for navigation and spatial memory. Furthermore, place cells exhibit the ability to adapt their

firing patterns in response to changes in sensory inputs. This adaptability manifests in the phenomenon of “remapping,” where place fields can shift or emerge in new locations if the environmental context changes, reflecting the brain's ability to update its representation of space (Colgin et al., 2008; Muller & Kubie, 1987). This dynamic property of place cells is essential for navigating through and understanding changing environments.

In addition to their role in spatial mapping, place cells are temporally coordinated with theta rhythms during active exploration, a phenomenon known as theta precession (O’Keefe & Recce, 1993). This coordination suggests a deeper level of neural processing, potentially linking spatial and temporal aspects of experience.

The involvement of place cells in episodic memory processes has also been proposed, given their contribution to contextual representation. By providing a neural substrate for the spatial context, place cells are believed to be fundamental in the formation of episodic memories, helping to anchor experiences in a specific spatial and temporal framework.

In summary, hippocampal place cells are a cornerstone of spatial cognition, offering a window into the neural mechanisms underlying navigation, memory formation, and the representation of space within the brain.

2.3.2 The sense of direction: Thalamic head-direction cells

Head direction (HD) cells, a fundamental component of the brain's navigational system, exhibit increased firing rates corresponding to the animal's head direction, irrespective of its location within the environment (Figure 3). These neurons are integral to providing a sense of directional orientation by integrating diverse sensory inputs, such as self-motion cues and external environmental landmarks (Cullen & Taube, 2017; Taube et al., 1990a). HD cells were first identified in the Postsubiculum (PoS) and have since been discovered in multiple

brain areas, including the dorsal tegmental nucleus (DTN), lateral mammillary nuclei (LMN), retrosplenial cortex (RSC), and the antero-dorsal nucleus of the thalamus (ADn), highlighting their widespread significance in the brain's navigation network (Bassett & Taube, 2001; Cho & Sharp, 2001; Stackman & Taube, 1998; Taube, 1995).

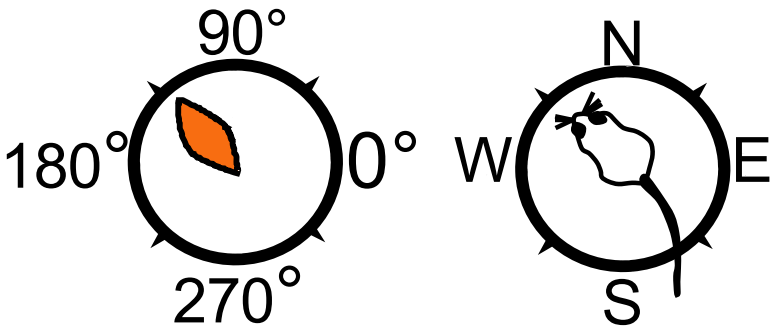

Figure 3 Head direction cells. Relationship between the firing rates of head direction (HD) cells and the animal's angular head direction, with an example showing the orange tuning curve (left) peaking when the animal faces northwest, indicating maximal firing at this orientation.

The processing of the HD signal commences within the semicircular canals, which provide crucial information related to head movement. This signal is then conveyed to the medial vestibular nucleus (MVN), where it is integrated with proprioceptive, visual, and vestibular inputs to encode angular head velocity (Cullen & Taube, 2017). In the DTN, approximately 75% of the cells are modulated by angular head velocity, indicating a direct relationship between cell firing rate and head velocity (Bassett & Taube, 2001). The signal then progresses to the LMN, where a significant proportion of cells are modulated by both angular head velocity and head direction (Stackman & Taube, 1998). The ADn receives this signal, with a majority of its neurons functioning as HD cells (Taube, 1995), and further transmits it to PoS and RSC, which are also populated with HD cells (Cho & Sharp, 2001).

Visual cortical areas contribute to the descending pathway, relaying through PoS and RSC. This pathway provides essential visual information for landmark cue processing and the resetting of preferred firing directions of HD cells. Each HD cell is characterized by a unique tuning curve, which depicts the head direction corresponding to the cell's firing. The peak firing rate, known as the preferred firing direction (PFD), is crucial for determining the cell's orientation specificity. Across the HD cell population, there is comprehensive coverage of all azimuthal directions, with directional firing ranges varying significantly among different brain areas in rodents (Taube et al., 1990a).

HD cells are distinguished not only by their firing properties but also by their ability to maintain internal coherence during external cue manipulations and to sustain network activity during sleep without external sensory input (Peyrache et al., 2015; Taube et al., 1990b). This resilience highlights the autonomy and stability of the HD cell network in encoding directional information. The functioning of HD cells has been extensively modeled within the framework of attractor network theory. This theory postulates an interconnected ring of HD cells, ensuring that cells with similar preferred directions are co-activated, while those with dissimilar directions are inhibited (Redish et al., 1996; Sharp et al., 2001). This dynamic interplay of excitation and inhibition is fundamental to the generation and maintenance of the HD signal, underscoring its critical role in spatial orientation and navigation.

2.4.Sharp-wave ripples and memory reactivation during sleep

The hippocampus, a crucial structure within the brain's limbic system, serves not only as a temporal bridge connecting cortical networks for the formation and long-term storage of memories but also plays a pivotal role in reactivating these cortical areas during rest non-REM) sleep. This replay is facilitated through a phenomenon known as sharp-wave ripples

(SWRs) (Buzsáki, 2015; Buzsáki et al., 1992), which are integral to memory consolidation processes (Girardeau et al., 2009; Peyrache et al., 2009, 2011; Sirota et al., 2003).

SWRs are characterized by brief, intense periods of heightened activity. The “sharp waves” typically lasting between 40 to 100 milliseconds, predominantly observed in the CA1 stratum radiatum during non-REM sleep. These sharp waves are accompanied by highly periodically synchronous spiking at frequencies ranging from 120 to 200 Hz, known as “ripples”, within the CA1 pyramidal layer (Buzsáki, 2015). Notably, while sharp waves and ripples occur in tandem, they are distinct events, each underpinned by different mechanistic processes.

Sharp waves are essentially excitatory events, originating in the hippocampal CA3 region. These waves propagate to the CA1 area via the Schaffer collateral pathway, a critical communication route within the hippocampus (Buzsáki, 2015). The transmission of this excitatory input from the CA3 region leads to a pronounced negative deflection in the CA1 stratum radiatum. This is followed by the generation of fast ripples in the CA1 pyramidal layer (Figure 4). The production of these ripples is modulated by basket cell interneurons, which play a crucial role in regulating the local circuit dynamics (Buzsáki et al., 1992; Schlingloff et al., 2014).

The intricate interplay between sharp waves and ripples in the hippocampus represents a complex neurophysiological process, essential for the consolidation of memories and the reorganization of neural networks. These events reflect the brain's ability to not only store but also to dynamically reprocess and integrate information during states of reduced sensory input, such as sleep. The study of SWRs, therefore, offers valuable insights into the fundamental mechanisms of memory consolidation and the role of the hippocampus in orchestrating these processes.

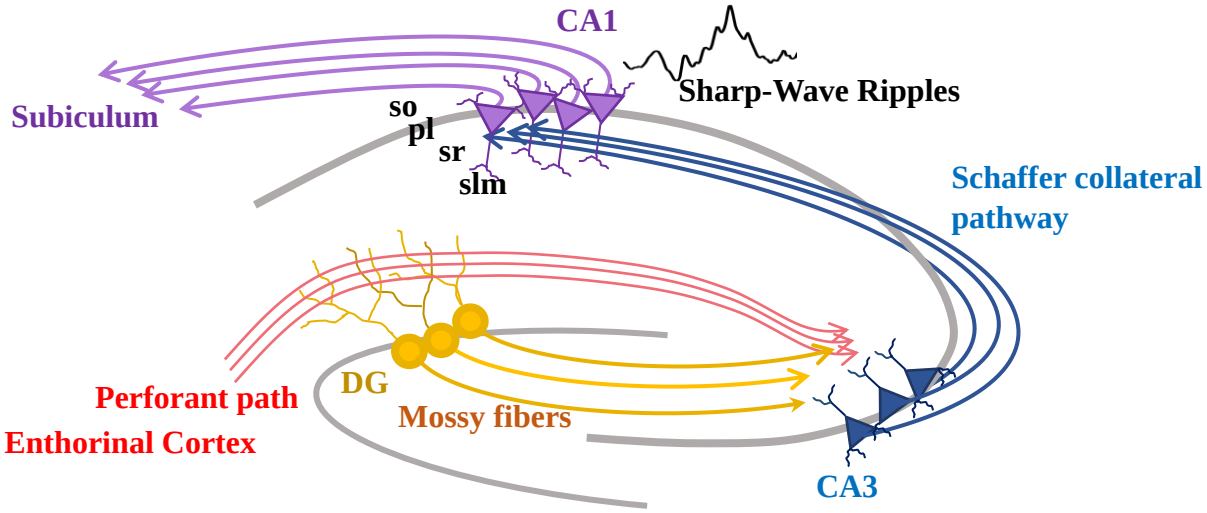

Figure 4 The hippocampal circuit. It shows the flow of synaptic connections among its key subfields: dentate gyrus (DG), CA3, and CA1 subregions. It delineates the trajectory of the perforant pathway originating from layer II of the Entorhinal cortex (EC), bifurcating into medial and lateral components that innervate the middle/outer molecular layers of the DG and the stratum lacunosum/moleculare of CA3. The mossy fiber pathway emerges from DG granule cells and converges onto the CA3 stratum lucidum, which in turn, through Schaffer collaterals, projects onto the dendritic layers of CA1, namely the stratum radiatum and oriens. The outbound signal from CA1 pyramidal neurons is relayed to the subiculum, ultimately closing the loop by projecting back to the EC, thus completing a critical circuit for hippocampal processing and output.

2.4.1 Replay of hippocampal place cell sequences during sleep

A growing body of evidence has characterized the phenomenon of hippocampal place cell sequence replay during non-REM sleep. This replay involves the reactivation of spike sequences by place cells that were initially activated during exploratory behavior, albeit at a significantly accelerated timescale (Lee & Wilson, 2002; Wilson & McNaughton, 1994). A particularly notable aspect of this replay is its temporal alignment with SWRs underscoring a complex interplay between different hippocampal processes (Skaggs & McNaughton, 1996) (Figure 5).

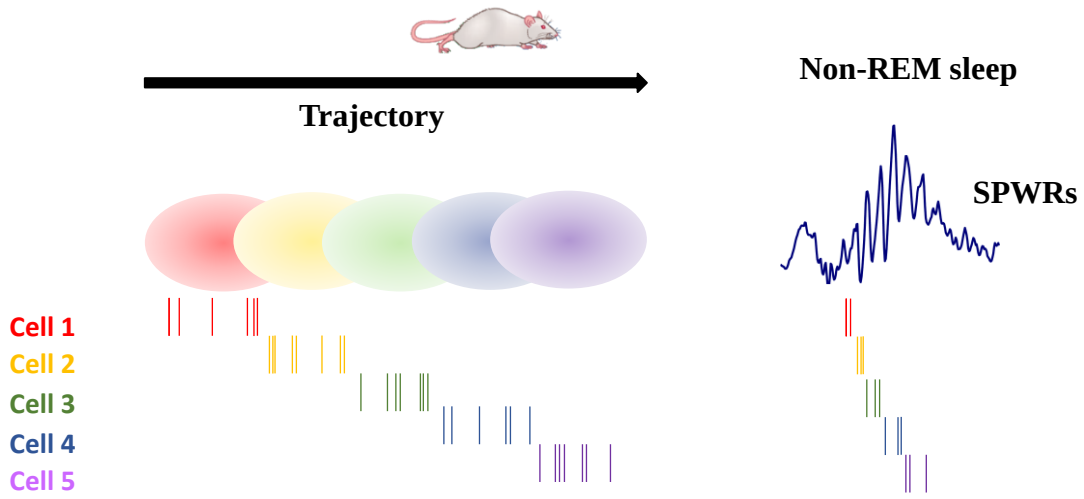

Figure 5 Hippocampal replay. Raster plot wherein each row corresponds to a distinct place cell, with individual lines denoting action potentials. The color-coded clusters within the plot signify place fields along a linear track. During the following non-REM sleep phases, we observed a temporally compressed reactivation of these spike sequences, mirroring those activated during prior exploratory behavior. Notably, this replay is synchronized with the occurrence of sharp wave ripples, implicating their potential role in memory consolidation processes.

Subsequent studies have expanded the understanding of replay, demonstrating its occurrence not only during sleep or periods of quiescence but also during various consummatory behaviors, such as eating and grooming, and in the context of action planning (Diba & Buzsáki, 2007; Foster & Wilson, 2006). This broader occurrence of replay highlights its potential role in diverse cognitive and behavioral contexts.

The replay of neuronal activity patterns following learning experiences has been implicated in the process of memory consolidation during offline states. Disruption of SWRs, and by extension, the associated replay, has been shown to impair the consolidation of spatial memory, suggesting a critical role of these processes in memory stabilization (Ego-Stengel & Wilson, 2010; Girardeau et al., 2009). Conversely, longer-duration SWRs have been correlated with enhanced memory consolidation and retrieval, indicating a dose-response relationship between SWR duration and memory performance (Fernández-Ruiz et al., 2019).

The genesis and modulation of hippocampal replay have been topics of significant debate. While SWRs are phase-locked to neocortical oscillations during non-REM sleep, suggesting a degree of external influence (Isomura et al., 2006; Sirota et al., 2003), neurons in the medial entorhinal cortex, a primary input to the hippocampus, demonstrate coherent firing patterns relative to wakefulness (Gardner et al., 2019; Trettel et al., 2019). This coherence suggests that hippocampal replay might include the reactivation of patterns formed during waking states (Ólafsdóttir et al., 2016). However, this perspective has been later challenged, with emerging evidence suggesting a more nuanced interplay between internal hippocampal dynamics and external inputs (O'Neill et al., 2017).

In summary, hippocampal replay during sleep represents a crucial element in the neural foundation of memory. Its interactions with SWRs, temporal synchronization with other brain regions, and modulation by both internal and external factors collectively contribute to the complex architecture of memory processing and consolidation.

2.4.2 Thalamic head-direction signal during sleep

The interplay between sleep and memory consolidation, particularly in the context of the thalamic head-direction (HD) signal, represents a relatively uncharted territory in neuroscientific research. While the broader fields of sleep's role in memory processes have been extensively studied, the specific involvement of the thalamic HD signal during sleep and its implications for memory replay and consolidation are areas that have only recently begun to garner attention.

The thalamus, particularly ADn, is one of the key regions where head-direction (HD) cells are found, which play a crucial role in maintaining a sense of direction during navigation. Recent studies have increasingly focused on the role of these HD cells during

sleep, shedding light on their potential contribution to the processes of memory replay and consolidation. The preserved activity of HD cells during sleep, particularly during non-REM stages, suggests a deeper, more nuanced role in memory processes. Peyrache et al. (2015) demonstrated that HD cells in the ADn maintain their coherence during sleep, indicative of a persistent representation of spatial orientation even in the absence of sensory input or movement. This preserved and internally generated activity implies that spatial information, encoded during wakefulness, is being consolidated during sleep (Peyrache et al., 2015). The continuous activity of HD cells during sleep challenges traditional views of sleep as a state of disengagement from the external environment. Instead, it proposes an active role of sleep in internal representation and consolidation of navigational experiences (Girardeau & Zugaro, 2011; Ji & Wilson, 2007; Peyrache et al., 2009; Rothschild et al., 2017). The ADn, through its sustained directional signaling, might facilitate the reorganization of spatial memories, integrating new experiences with existing cognitive maps (Peyrache et al., 2017).

The hippocampal-thalamic interactions during sleep are fundamental to memory consolidation. The precise timing of HD cell firing in relation to hippocampal ripples suggests a coordinated effort in processing and strengthening spatial memories (Buzsáki, 1989). This temporal coupling supports the theory that thalamic and hippocampal networks work in tandem during sleep to refine and solidify spatial memories (Peyrache, 2022).

3. Objectives

The investigation of hippocampal replay and its modulation by external neural inputs, such as from the entorhinal cortex, is a complex challenge, necessitating simultaneous recordings from large neuronal populations in these areas (Ólafsdóttir et al., 2016). However, HD cells present a unique and more accessible avenue to explore these dynamics. My PhD project is

thus focused on examining the role of the HD signal in influencing the replay of spatial trajectories encoded by hippocampal place cells during both wakefulness and sleep. This research is structured into three specific objectives, aiming to provide deeper insights into the neural mechanisms of spatial memory and its consolidation.

- Objective 1: To elucidate the extent of coordination between ADn-HD cells and hippocampal CA1 place cells during non-REM sleep, thereby assessing the synchronicity of their activity in relation to spatial memory consolidation.

- Objective 2: To characterize the patterns of reactivation of hippocampal CA1 place cells and ADn-HD cells during non-REM sleep phases, contributing to an understanding of the neural replay mechanisms implicated in spatial memory.

- Objective 3: To investigate the nature and informational content of the ADn-HD cell reactivations during non-REM sleep, aiming to delineate the specific elements of spatial experience that are processed during these reactivation episodes.

4. Hypothesis

- Hypothesis 1: Following the performance of a spatial navigation task, there will be a significant coordination in the activity of ADn-HD cells and CA1 place cells during non-REM sleep, reflecting a neural substrate for spatial memory consolidation.

- Hypothesis 2: The co-firing patterns of ADn-HD cells that are established during the spatial task will exhibit reactivation during subsequent non-REM sleep, suggesting a replay mechanism that contributes to the stabilization of spatial memory.

- Hypothesis 3: The HD signal during non-REM sleep will selectively reactivate components of the spatial memory task, indicating a targeted retrieval and strengthening of task-specific spatial information.

5. Methods

5.1. Animals

In the present study, we utilized a cohort of C57BL/6JxFVB hybrid mice (12 weeks old). Prior to training in behavioral tasks, the mice were subjected to a controlled food deprivation protocol, which was carefully designed to reduce their body weight to 85% of the baseline observed under free-feeding conditions. This approach aligns with established practices in behavioral neuroscience to motivate performance in cognitive tasks without compromising animal welfare (Walf & Frye, 2007). Following the acclimatization period, the mice were systematically trained on a Y-maze alternation task (described below), a paradigm extensively employed in the assessment of spatial memory and cognitive flexibility (Deacon & Rawlins, 2006). The Y-maze apparatus consisted of an elevated structure with a central platform measuring 15 cm in diameter, from which three arms extended, each 25 cm in length and 6 cm in width (Figure 6).

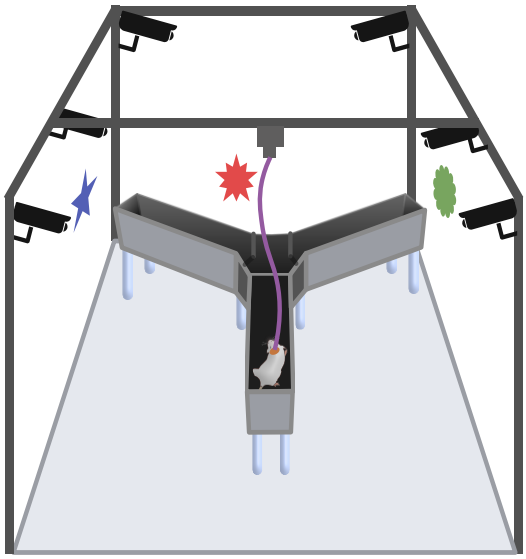

Figure 6 electrophysiological setup. Schematic illustration of electrophysiological recordings in freely moving mice performing a spatial memory task. The position of the animals on the Y-maze is recorded by a tracking system conformed by 8 cameras capable to detect spheres reflective markers attach to the animal's implant.

This configuration permits the evaluation of spontaneous alternation behavior, serving as an indicator of working memory and spatial navigation capabilities (Lalonde, 2002).

5.2. Y-maze Alternation task

The goal of the task is for the mouse to alternate between two different arms in the Y- maze to obtain a reward. Two different versions of the alternation task are used in this project, forced alternation and free alternations tasks.

5.1.1 Forced alternation task.

The Forced Alternation Task, a behavioral paradigm designed to assess spatial working memory and decision-making, was employed in this study. The task starts with a forced choice run (trial one), during which the subject was presented with a single accessible arm containing a reward, while the alternative arm was obstructed. The configuration of the Y-maze ensured that only the arm containing the reward was open. Subsequently, for trial two, the previously inaccessible arm was unveiled, permitting the mouse entry to secure the reward, concomitantly, the arm that was open in the initial trial was now closed. Each trial was initiated with the animal positioned in the starting arm, from which it navigated to retrieve the reward, thereafter, returning to the starting point.

Prior to the commencement of the Forced Alternation Task, a habituation protocol was implemented. Herein, each mouse was introduced to the Y-maze environment for a duration of 15 minutes, during which it was free to explore and consume a reward (0.1 ml of chocolate milk) positioned in all three arms. The frequency of reward consumption was meticulously recorded, with a benchmark set at a minimum of 20 consumptions for two sequential days as the criterion for progression to the subsequent training phase. Should an animal exhibit reluctance or inactivity during the initial 10 minutes, it was gently returned to the familiar confines of its home cage.

During the subsequent alternation training phase, each mouse underwent a 30-minute session daily, wherein a predetermined goal arm was baited with a 0.1 ml aliquot of chocolate milk. To maintain a sterile environment and mitigate olfactory cues, the maze was sanitized with ethanol following each session, aligning with the guidelines stipulated by Deacon and Rawlins (2006), and further endorsed by the protocols outlined in the comprehensive manual of behavioral neuroscience methods (Buccafusco, 2009).

5.1.2 Y-maze Free Alternation Task

This second version of the Y-maze alternation task leverages the intrinsic exploratory drive of rodents. In the initial trial, mice are placed at the base of the start arm and presented with a binary choice between two open arms. One of these arms conceals a reward, while the other serves as a decoy. Subsequent to the initial choice, the second trial necessitates that the mice utilize their spatial memory to navigate to the previously unexplored arm, thus demonstrating their ability to recall and discriminate between the familiar and novel environments. This spontaneous alternation behavior, wherein rodents exhibit a natural propensity to explore new areas, is indicative of intact spatial working memory, a cognitive process intricately linked to hippocampal and thalamic function (Aggleton et al., 1996; Conrad et al., 1996).

5.3. Surgical procedures and silicon probes implantation

All the procedures were approved by the Canadian Council on Animal Care and approved by the Montreal Neurological Institute's Animal Care Committee. The mice, following a period of pre-training in the Y-maze, were subjected to surgical implantation of high-density silicon probes (Neuronexus) while under isoflurane anesthesia to ensure minimal distress. Each silicon probe, consisting of four shanks with 200-µm inter-shank separation, was equipped with eight recording sites per shank (Buzsáki, 2004). These probes were affixed to precision microdrives, allowing for the meticulous adjustment necessary for optimal recording of single-unit neuronal activity and local field potentials (LFPs).

In each mouse, two silicon probes were implanted: one within the ADn, and the other in the hippocampal CA1 region, with both probes situated in the left cerebral hemisphere and

inserted perpendicularly to the midline (Figure 7A). The stereotaxic coordinates for the ADn implantation were as follows: antero-posterior (AP) -0.46 mm, medio-lateral (ML) -0.75 mm, and dorso-ventral (DV) -1.5 mm. For the CA1 region, the coordinates were set at AP −1.8 mm, ML −1.4 mm, and DV 0.5 mm (Figure 7B). To establish an electrical reference point, a ground wire composed of silver (127 μm in diameter) was positioned above the cerebellum.

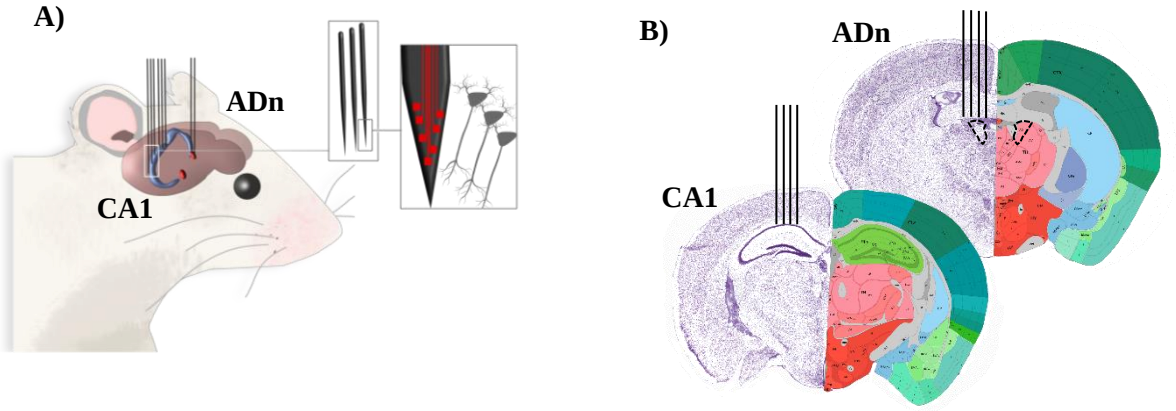

Figure 7 Implantation of Silicon Probes. A) Pre-trained mice were implanted with high-density silicon probes targeting the anterodorsal nucleus (ADn) of the thalamus and the CA1 region of the hippocampus. **B)** Coronal brain sections showing the distinct trajectories of the 4-shank recording electrode in CA1 (left) and ADn (right).

Post-surgical recovery spanned 5–7 days, during which the ADn probe was progressively lowered in increments of 70–140 μm daily until the detection of the first single units. Concurrently, the CA1 probe was carefully adjusted to align with the pyramidal layer, identifiable by the presence of pronounced ripple oscillations. Neurophysiological data acquisition during sessions was conducted via a 64-channel Intan RHD2000 System, capturing continuous signals at a sampling rate of 20 kHz with a 16-bit resolution, and utilizing analog multiplexing. The wide-band signal was subsequently downsampled to 1.25 kHz to extract the LFP for analysis (Buzsáki et al., 2015).

5.4. Behavioral protocol and recording sessions.

The recording sessions were structured to encompass both Y-maze forced and free alternation tasks, with each task spanning a duration of 30 minutes. Specifically, each Y-maze task was both preceded and succeeded by a one-hour sleep session, cumulatively amounting to three sleep sessions per experimental sequence (Figure 8). This design allows for the observation of neural patterns associated with memory consolidation processes during sleep following task engagement (Smith & Mizumori, 2006). All experimental procedures were conducted during the daylight hours to maintain consistency with the mice's natural light-dark cycle (Wright et al., 2002).

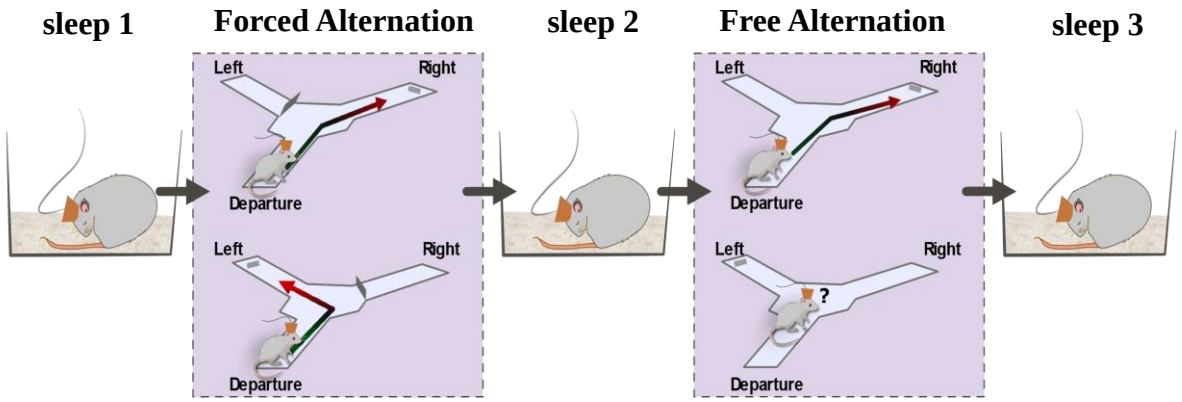

Figure 8 Design of the experimental protocol. The recording sessions included Y-maze forced and free alternation tasks, each lasting 30 minutes and by one-hour sleep sessions before and after, resulting in three sleep sessions**.**

5.5. Tracking position

The spatial positioning of the animals within the Y-maze was determined through a tracking system (*Optitrack*), comprising eight high-definition cameras, each with the capacity to record at a resolution of 120 frames per second. This system enabled the precise monitoring of the subjects' locomotor trajectories within the experimental apparatus. To facilitate accurate tracking, four spherical reflective markers were affixed to the headstage attached to each mouse. These markers were strategically positioned to optimize the detection by the camera system (Figure 9).

The positional data captured by this array of cameras was then relayed to the OptiTrack Motive software (version 2.1.1), a platform offering high precision and reliability in motion tracking. Within this software environment, the spatial coordinates of the markers—specifically, the X, Y, and Z values—were computed, allowing for the reconstruction and analysis of the animals' navigational patterns in three-dimensional space.

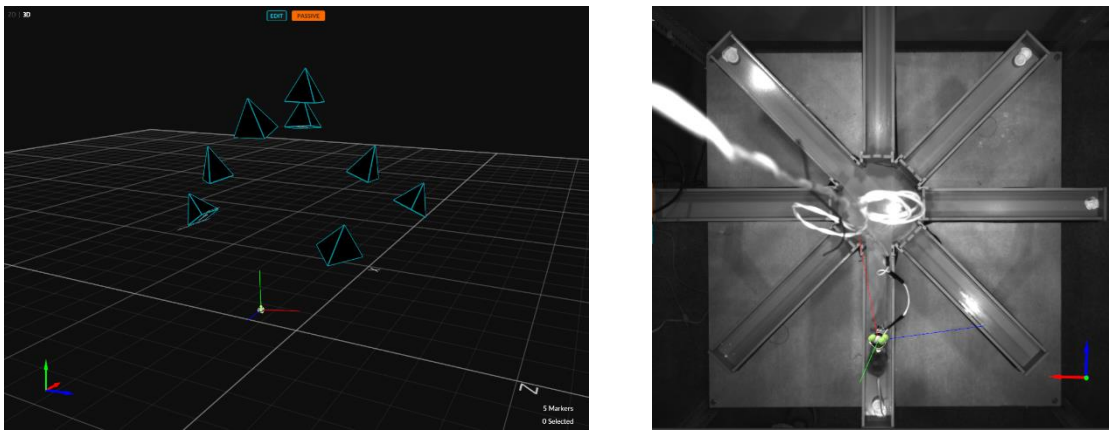

Figure 9 OptiTrack system. It tracks 3D movements by capturing the position of reflective markers using an array of synchronized cameras.

5.6. Neurophysiological signals pre-processing and data analysis

5.6.1 Spike sorting.

The acquisition of neurophysiological data necessitates rigorous preprocessing to discern individual neural units, a task accomplished through the deployment of an automated spike sorting algorithm known as Kilosort (Pachitariu et al., 2016). This advanced algorithm leverages the power of high-dimensional cluster analysis to efficiently segregate the recorded spike events, thereby facilitating the identification of single-unit activities with remarkable precision (Pachitariu et al., 2016) (Figure 10).

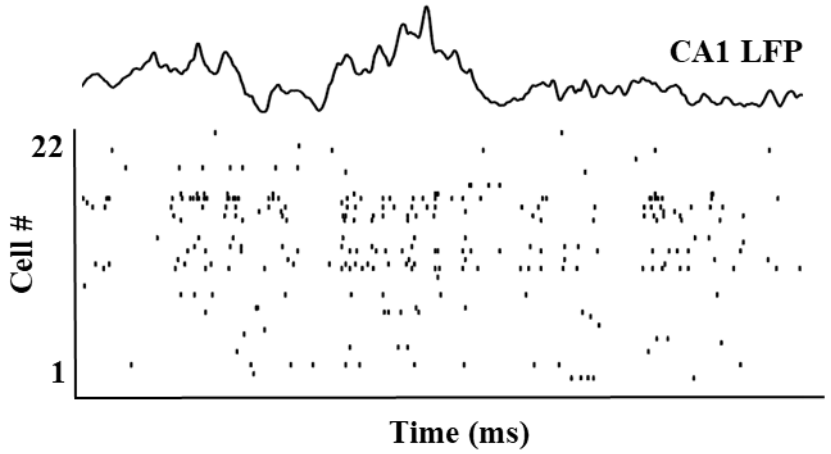

Figure 10 Electrophysiological recording. Single-unit action potentials, along with Local Field Potentials (LFPs), are recorded to capture both the discrete neuronal firing events and the collective synaptic activity within the neural tissue.

Following the initial computational sorting, the isolated units undergo meticulous manual curation. This crucial step is conducted with Klusters (Hazan et al., 2006), a tool designed for the detailed scrutiny of electrophysiological data. The validation of single-unit isolation is accomplished through a comprehensive examination of auto-correlograms and spike waveform characteristics, ensuring the accuracy of unit classification and the integrity of subsequent analyses.

5.6.2 Sleep scoring.

The classification of sleep states within this study was conducted through a comprehensive analysis of the hippocampal local field potential (LFP), specifically examining the theta-to-delta power ratio, in conjunction with electromyographic (EMG) data, following the methodologies delineated by Grosmark and Buzsáki (2016). These analyses were facilitated by the utilization of TheStateEditor, a component of the Buzsáki Lab's suite of tools designed for the processing and classification of neurophysiological data (Buzsáki Lab, n.d.).

Rapid eye movement (REM) sleep was characterized by a distinct electrophysiological signature, prominently featuring high-amplitude oscillations within the theta (4–9 Hz) and gamma (33–55 Hz) frequency bands. Conversely, non-rapid eye movement (non-REM) sleep was identified by a marked reduction in gamma oscillatory activity and a prevalence of high-amplitude delta (1–4 Hz) waves. Wakefulness was discerned by the presence of high-amplitude activity in both gamma and theta frequency ranges. Complementary to these LFP-based criteria, EMG recordings were employed to detect periods of muscular atonia, thereby corroborating the identification of REM sleep phases (Figure 11).

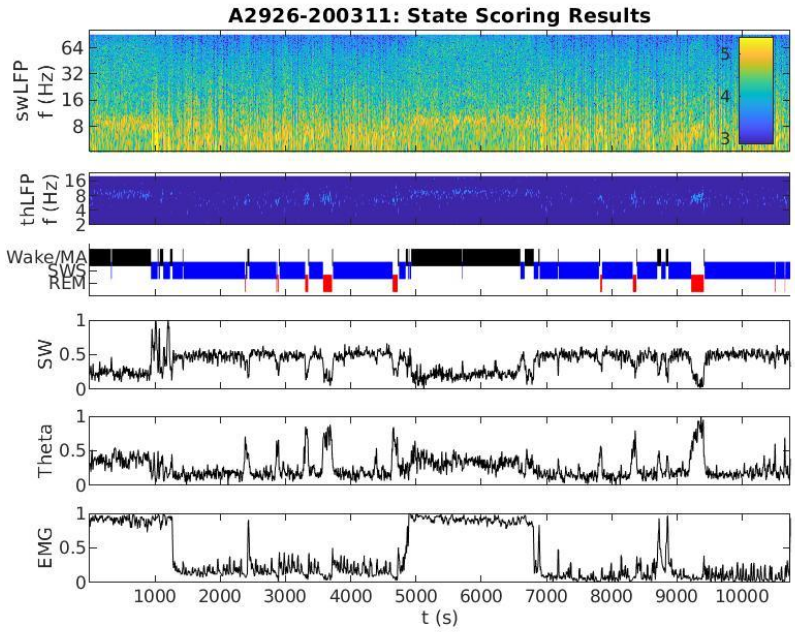

Figure 11 Sleep scoring. Sleep state classification based on hippocampal LFP's theta-to-delta ratio and EMG data: REM sleep (red) featured high theta and gamma oscillations, non-REM sleep (blue) showed prominent delta waves with low gamma activity, and wakefulness (black) was marked by high gamma and theta oscillations, with EMG-confirmed muscle atonia indicating REM sleep.

5.6.3 Ripple detection.

The detection of SWR events within the CA1 region's LFP was executed through a sequence of signal processing steps as described in Viejo and Peyrache, 2020. Initially, the CA1 LFP signal was subjected to a Gaussian bandpass filter, restricting the frequency range to 80-300 Hz, optimal for isolating ripple oscillations. Following this, the signal was squared to emphasize the power within this band and subsequently smoothed via a digital filter with a specified window length of 11 to attenuate transient noise artifacts. The processed signal underwent normalization through z-scoring, employing the calculated mean and standard deviation of the session-specific LFP distribution. The ensuing normalized squared signal was subjected to a thresholding protocol, delineating candidate ripples that surpassed the amplitude of 3 to 7 standard deviations from the mean. This range was selectively adjusted to 2 to 5 standard deviations in sessions characterized by ripples of lower amplitude, ensuring the sensitivity of the detection algorithm. Each candidate ripple was then vetted based on duration, conserving only those events that spanned between 25 ms and 350 ms. This constraint facilitated the exclusion of aberrant or spurious signals not representative of true SWR events.

In the final stage of analysis, proximate ripples occurring within 30 ms of one another were merged, being considered a single cohesive SWR event. This methodological approach ensured that closely sequential ripples were appropriately classified as singular neural

occurrences, reflecting the inherently rapid succession of these phenomena (Viejo & Peyrache, 2020)

5.6.4 Explained Variance

The objective of this investigation is to elucidate the mechanisms of memory reactivation during sleep, a process integral to the consolidation of experiential memories. To achieve this, we computed the Explained Variance (EV), a methodological framework that quantifies the degree of similarity between neuronal firing-rate correlation matrices from task-engaged (RUN) and subsequent sleep (POST) epochs (Kudrimoti et al., 1999). This is accomplished by adjusting for the baseline correlations established between the task (RUN) and the preceding restful state (PRE). Such a comparative analysis is pivotal, as it allows for the temporal and state-dependent examination of how prior experiences can modulate the neural firing-rate correlation patterns. To quantify the explained variance (EV) in the post-task sleep state (POST) attributable to a preceding track-running experience (RUN), we applied a multiple correlation analysis utilizing the square of partial correlation coefficients. This analysis incorporated the lower diagonal elements from the firing-rate correlation matrices of the pre-task (PRE), task (RUN), and post-task (POST) periods as variables, thereby yielding a robust statistical measure of the influence of awake experiences on sleep-based neural processing (Kleinbaum et al., 1988). We used the following formula:

$$EV = \left(r_{RUN,POST} - r_{RUN,PRE} * r_{POST,PRE}\right) / sqrt\left(\left(1 - r_{RUN,PRE}^2\right) * \left(1 - r_{POST,PRE}^2\right)\right)^2$$

Specifically, we looked at a 60-minute period of sleep before the task, referred to as the PRE phase, and a 30-minute period during the Y-maze task, termed the RUN phase, as the predictors in our model. The outcome variable in this analysis was the neural correlation during the 60-minute sleep period following the task, known as the POST phase. To discern

the specific impact of the task on post-task sleep, we accounted for the baseline neural correlations from the PRE phase, essentially removing their influence to reveal the pure effect of the RUN phase on the POST phase neural activity correlations. This method allowed us to isolate and understand how the task experience influences neural patterns during the subsequent sleep period (Kudrimoti et al., 1999).

5.6.5 Bayesian decoding

To accurately predict the head direction of the animal across wakeful and sleep states, we utilized Bayesian decoding (Zhang et al., 1998), a statistical technique that leverages the spiking activity of HD cells within specific time windows. This method enables the computation of the likely head directions, knowing the population spike counts. The underlying formula for this computation, central to our analysis, is structured as follows:

$$P(HD|spikes) = \big(P(spikes|HD) * P(HD)\big)/P(spikes)$$

Here, $P(HD|spikes)$ represents the posterior probability of a particular head direction given the observed spiking activity, $P(spikes|HD)$ denotes the likelihood of observing the spike count given a head direction (obtained from the tuning curve), $P(HD)$ is the prior probability of the head direction (i.e. the occupancy), and $P(spikes)$ is the probability of the spike count irrespective of head direction (i.e. the average firing rate). The decoded head-direction correspond to the head-direction for which $P(HD|spikes)$ is maximal (i.e. the *argmax*).

5.6.6 Linear decoding

It's crucial to acknowledge that Bayesian decoding inherently incorporates pre-existing knowledge about the system into its analysis (tuning curves and assumption that spike trains are Poisson processes), which might introduce a certain degree of bias in its decoding process. To counterbalance this and provide a robust validation of our decoding approach, we implemented a linear decoding model to process spike data from HD cells in the ADn across both wakeful and sleep states. Unlike Bayesian decoding, the linear model bases its predictions of HD purely on observed spike rates, without relying on prior data knowledge. This model processes the input neural data by normalizing and converting it into a format suitable for prediction. During the training phase, the model's accuracy is evaluated by comparing the decoded HD against the actual HD data. Such a comparison is instrumental in determining the model's effectiveness and guiding the training procedure. This approach ensures a comprehensive and unbiased interpretation of neural signals and will be useful to validate findings obtained with Bayesian decoders.

5.6.7 Isomap projection

The isomap projection enables the reduction of high-dimensional data into a lower-dimensional space for easier visualization and interpretation, while preserving the intrinsic geometric structure of the data (Tenenbaum et al., 2000). When applied to neuronal data, it can reveal the underlying topological organization of the population firing (Chaudhuri et al., 2019; Viejo & Peyrache, 2020). Specifically, we binned the trains in 200 ms intervals and subsequently applied a square-root transformation. This transformation was crucial to normalize the data, accounting for variance in spike rates across different neurons.

The normalized spike rates from all HD cells recorded simultaneously in the ADn were then utilized as input data for the Isomap algorithm. We chose a parameter of 30 neighbors for the Isomap algorithm to optimally balance local and global data structures. The output from the Isomap algorithm revealed ring manifolds, which effectively captured intrinsic topology of HD cell population activity. To enhance the clarity of our data representation, we employed a color-coding scheme on these ring manifolds. Each color on the manifold corresponded to the actual head direction of the animal for each respective time bin. Decoding is then performed by computing the angular coordinate of each point on the 2D projected data. This third decoding strategy will be used to further validate our findings regarding the "virtual" HD signal during sleep.

6. Results

6.1 Coupling between CA1 place cells and ADn head direction cells during sleep.

Animals (n = 4 mice) were implanted with high-density silicon probes targeting ADn (12.2 ± 6.6 s.d. single units per session) and the CA1 region of the hippocampus (14.2 ± 7.9 s.d. single units per session) (Figure 12 A). Population activity was then recorded both during wakefulness and sleep (Figure 12 C and E). Animals were food-deprived and pre-trained on a forced alternation task on a Y-maze for fifteen days. Following a week of post-surgical recovery and an additional week of reacclimatization training, we recorded the animals during forced and free alternation tasks and three 1-hour sleep sessions (non-REM 1-3) before and after each task. In the forced alternation task, both arms were baited at each visit in addition to the departure arm before the start of the next trial. In the free alternation, mice had to learn to freely alternate between left and right arms (a spontaneous behavior in rodents) to obtain a

reward (Figure 12 B). The departure arm was baited after each successful trial. The consumption of a reward at the departure arm is a strong attentional distractor, requiring the animal to keep a memory trace of the previously visited arm. As expected, a vast majority of ADn neurons were modulated by head-direction (Figure 12 D and E) and CA1 neurons showed place fields as the animal runs on the Y-maze (Fig. 12 F and G). ADn-HD cells and CA1 place cells continued to exhibit activity throughout the sleep period (Fig. 12 H). To investigate the synchronization between ADn and CA1 groups during sleep, we calculated pairwise cross-correlograms between ADn and CA1 spike patterns. We observed a consistent rise in CA1 firing rates 50-100ms following ADn spikes (Fig. 12 I), regardless of the sleep session (Fig. 12 J).

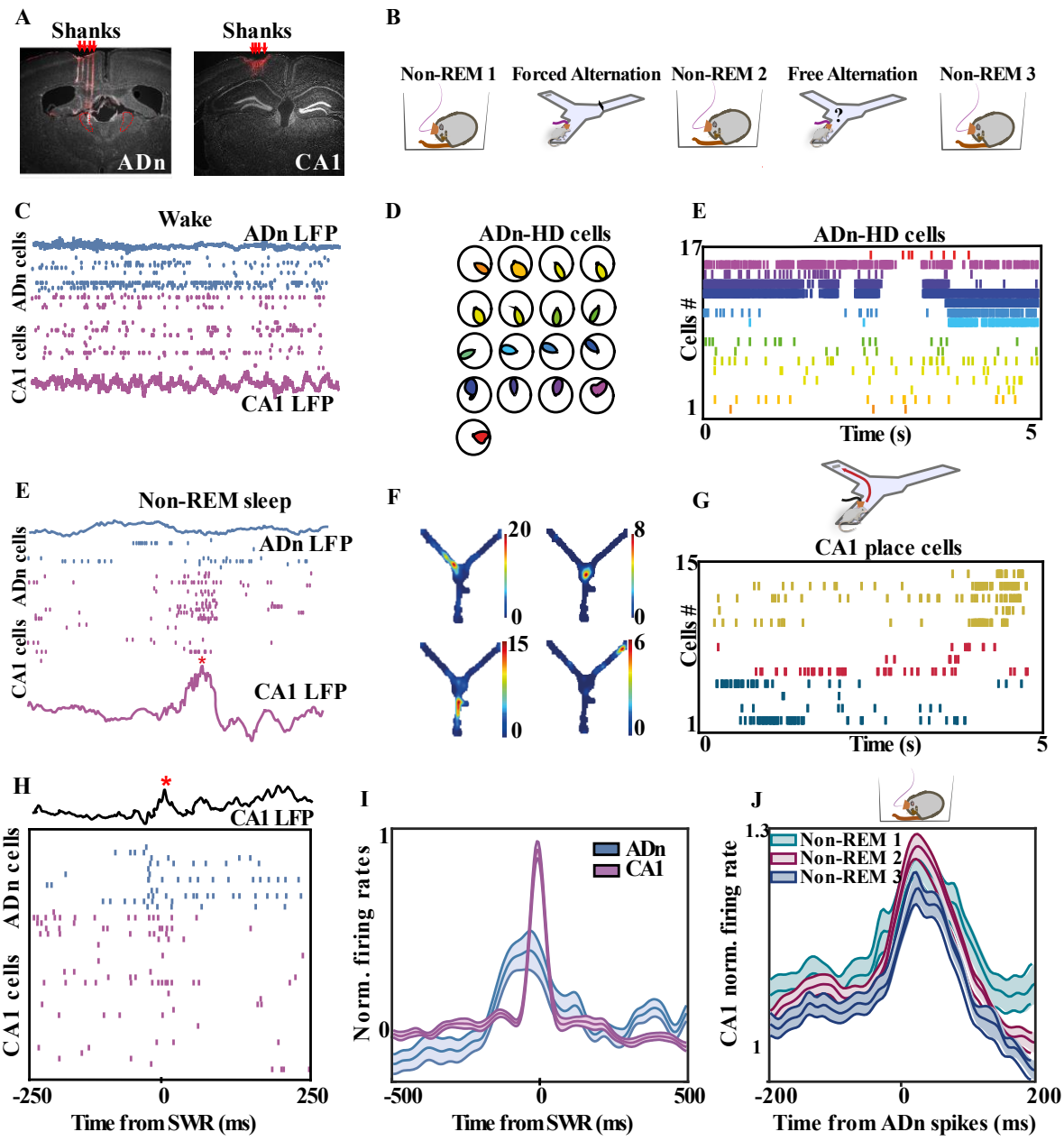
A
Shanks
Shanks
ADn
CA1
B
Non-REM 1
Forced Alternation
Non-REM 2
Free Alternation
Non-REM 3
C
Wake
ADn LFP
ADn cells
CA1 cells
CA1 LFP
D
ADn-HD cells
E
ADn-HD cells
17
Cells #
1
0
Time (s)
5
E
Non-REM sleep
ADn LFP
ADn cells
CA1 cells
CA1 LFP
F
20
0
8
0
15
0
6
0
G
CA1 place cells
15
Cells #
1
0
Time (s)
5
H
CA1 LFP
ADn cells
CA1 cells
-250
0
250
Time from SWR (ms)
I
1
Norm. firing rates
0
ADn
CA1
-500
0
500
Time from SWR (ms)
J
1.3
Non-REM 1
Non-REM 2
Non-REM 3
CA1 norm. firing rate
1
-200
0
200
Time from ADn spikes (ms)

Figure 12 Coordinated activity between ADn head direction cells and CA1 place cells across wakefulness and sleep states. **A)** Coronal sections of the mouse brain displaying the silicon probe shanks' trajectories (highlighted in red) targeting ADn and CA1. **B)** Y-maze's schematic for both forced and free alternation tasks, alongside the experimental protocol's design. **C) L**ocal field potential (LFP) traces alongside the spiking activity recorded from ADn (blue) and the hippocampal CA1 region (purple) during wakefulness. **D)** Tuning curves of head direction cells from the ADn, organized according to their preferred firing direction. **E)** Raster plot depicting the activity of ADn head direction (HD) during a single trial on the Y-maze. **F)** LFP traces and spiking activity in ADn (blue) and CA1 (purple) during sleep. **G)** Examples of place fields from four distinct CA1 place cells, each exhibiting firing at different locations along the Y-maze. H) CA1 principal cell firing patterns are presented for a single trial in the Y-maze. **I)** Broad-spectrum local field potential recording from the CA1 region, with a red asterisk marking a sharp wave-ripple. At the bottom, the panel displays the spiking activity of both ADn-HD cells and CA1 neurons during non-REM sleep. **J)** cross-correlation between ADn-HD cells and CA1 neurons is plotted to illustrate their temporal relationship around the occurrence of sharp wave-ripples. **K)** Normalized firing rates of CA1 place cells during successive episodes of non-REM sleep: 1 (green), 2 (pink), and 3 (blue),

6.2 Thalamic anterodorsal nucleus-head direction signal leads hippocampal CA1 reactivation during Non-REM Sleep .

To investigate the phenomenon of neuronal reactivation during off-line states, we employed an analytic approach known as explained variance (EV). This technique quantifies the degree of similarity between neuronal correlation patterns observed during active task performance and those during subsequent sleep periods, adjusting for any inherent correlations that existed between the task and preceding sleep phases. To establish a baseline for reactivation across individual sessions, we computed the reversed explained variance (REV), in which the cell pair coherency from pre-sleep and post-sleep sessions is transposed, essentially inverting the temporal progression. Reactivation was subsequently quantified as the difference between EV and REV, offering an accurate measure of neural pattern reactivation. We observed no reactivation of the CA1 cell assembles during sleep sessions after both tasks, a Repeated Measures Two-Way ANOVA revealed no statistically significant differences between EV and

its control REV during Non-REM sleep 2 (P = 0.82), Similarly, the analysis of EV and REV during Non-REM sleep 3 showed no significant differences (P = 0.22). These findings indicate the lack of reactivation of CA1 place cells during the sleep followed by an alternation task, free or forced, on a highly familiar maze. In contrast, we observed a significant reactivation of ADn-HD cell ensembles exclusively following the free alternation task, during non-REM sleep 3 (P = 0.003). Conversely, such reactivation was not detected after the forced alternation task, during non-REM sleep 2, (P = 0.47). Finally, we assessed the synchronized reactivation of CA1 place cells and ADn-HD ensembles. Statistical analysis showed significant reactivation following the free alternation task during non-REM sleep 3 (P = 0.04). However, such reactivation was not observed after the forced alternation task, in non-REM sleep 2 (P = 0.20)

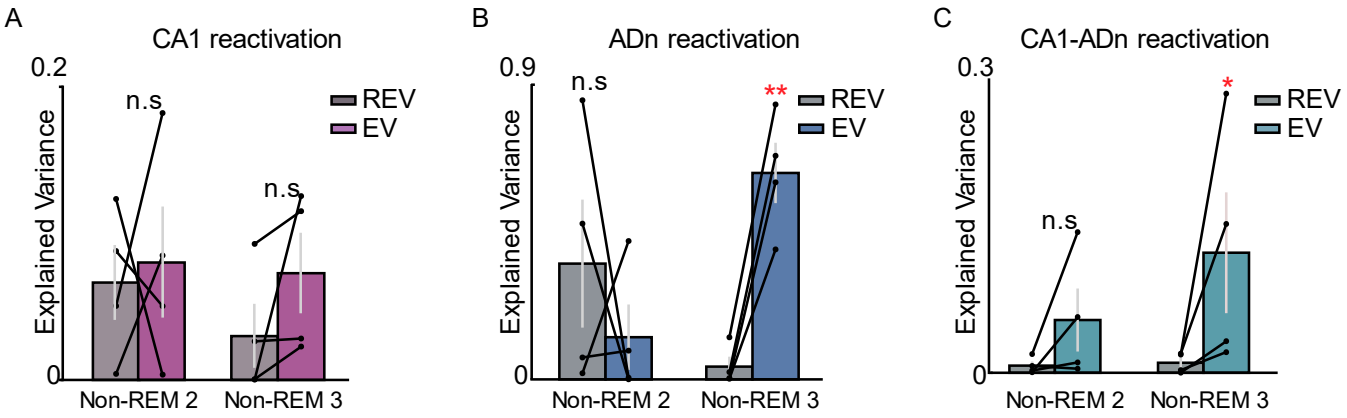

Figure 13 Thalamic and hippocampal reactivation during non-REM sleep. A) Reactivation profiles of CA1 place cells and **B)** ADn-HD cells during non-REM sleep following the forced alternation task (non-REM 2) and free alternation task (Non-REM 3), with reverse explained variance shown in gray, and the explained variance depicted in purple and blue, respectively. **C)** Coordinated reactivation of CA1 place cells and ADn-HD cell ensembles, showed in green. Statistical differences were determined using Repeated Measures Two-Way ANOVA, followed by Fisher LSD post hoc analysis. (*) indicates statistical significance at P<0.05, (**) indicates statistical significance at P<0.005.

6.3 Bayesian decoding reveals non-homogeneous distribution of decoded angles during Non-REM sleep

To explore which aspects of the spatial memory task are encoded during wakefulness and reactivated during subsequent sleep, we implemented Bayesian decoding. Utilizing wakeful HD tuning curves and ADn-HD cell spiking data during wakefulness (Figure 14 A, C), and sleep (Figure 14 E, G), we calculated posterior probabilities for a continuum of head directions during both alternation tasks (Figure 14 B, D) and the subsequent non-REM sleep periods (Figure 14 F, H). This approach enabled the quantification of the directional information encoded and retrieved across different brain states.

In order to quantitatively measure the overlap and similarity between the distribution of probability values of the decoded angles during the tasks and their subsequent non-REM sleep session, we employed the Bhattacharyya distance and the associated coefficients. The Bhattacharyya distance was computed using the formula:

$$BD = -\ln\left(sum\left(sqrt\left(p(x) * q(x)\right)\right)\right)$$

Where $p(x)$ and $q(x)$ represent the probability densities of the two distributions compared. Then, and the Bhattacharyya coefficient was subsequently derived as:

$$BC = e^{-BD}$$

Where BD is the Bhattacharyya distance, to quantify the degree of overlap between these distributions. The use of Bhattacharyya coefficients, derived from the Bhattacharyya distance, provides a scalar measure of similarity, with values closer to 1 indicating greater overlap. The average Bhattacharyya coefficients (mean ± standard error of the mean, SEM) between the forced alternation task and non-REM sleep 2 was 0.97 ± 0.01. The mean of the calculated Bhattacharyya coefficients for the comparison between the free alternation task and non-REM

sleep 3 was 0.98±0.01. Wilcoxon signed-rank tests to these coefficients showed non statistical differences between the distribution of the decoded angles in each session P>0.05.

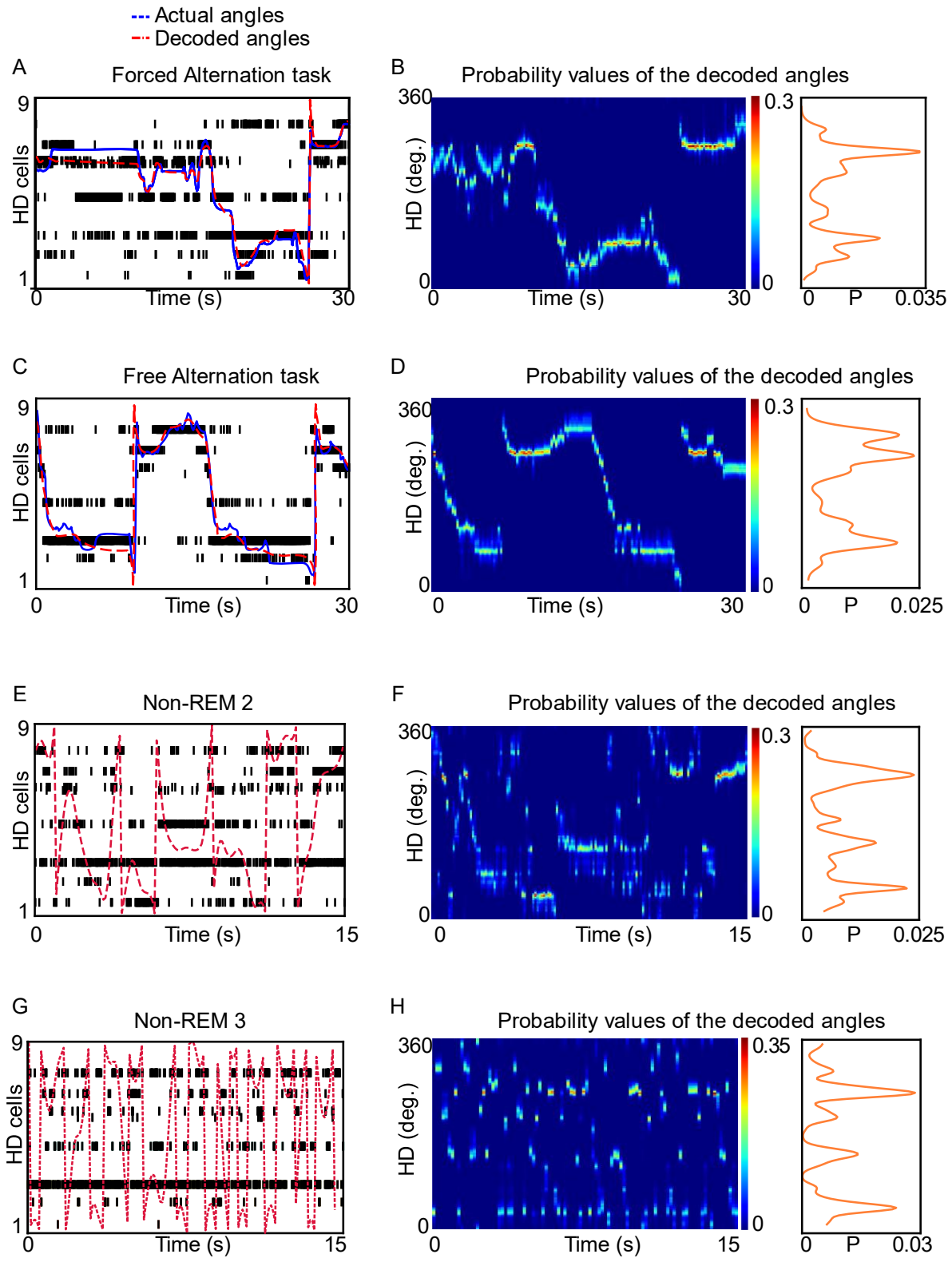

Figure 14 Bayesian Decoding of Head Direction signal. A) The left panel exhibits an example of the spiking activity of head direction (HD) cell ensembles during the performance of the forced alternation task, and **B**) during the free alternation task, which illustrates both the actual (depicted by a blue line) and the decoded (indicated by a red line) head directions. **C)** Spiking activity of the subsequent non-REM sleep sessions (panels **C** and **D**). The central panel features a heatmap that delineates the probability values of the decoded head direction angles across both wakefulness and non-REM sleep states. The right panel shows the sum of probabilities for each decoded head direction angle during wakefulness and non-REM sleep.

6.4 Linear Decoding Corroborates Bayesian Observations of Non-Uniform Angular Distributions During Non-REM Sleep.

To validate our decoding methodology, we complemented Bayesian techniques with a linear decoding model that derives head direction predictions from spike rates of ADn cells, without the need for prior data. By analyzing spike rates of ADn-HD cells observed during wakefulness and sleep phases (Figure 15 A, C, E, and G), we computed posterior probabilities for a range of head directions in both tasks and their subsequent non-REM sleep episodes, (Figure 15 B, D, F, and H).

The Bhattacharyya coefficients, consistent with our Bayesian decoding observations, indicated no significant differences, reinforcing the stability in the representation of head direction across various conditions. Specifically, the average Bhattacharyya coefficient for the transition from the forced alternation task to non-REM sleep phase 2 was recorded at 0.941 ± 0.02, while the comparison between the free alternation task and non-REM sleep phase 3 yielded a mean coefficient of 0.943 ± 0.02. Wilcoxon signed-rank tests showed non statistical differences between the distribution of the decoded angles in each session $P>0.05$.

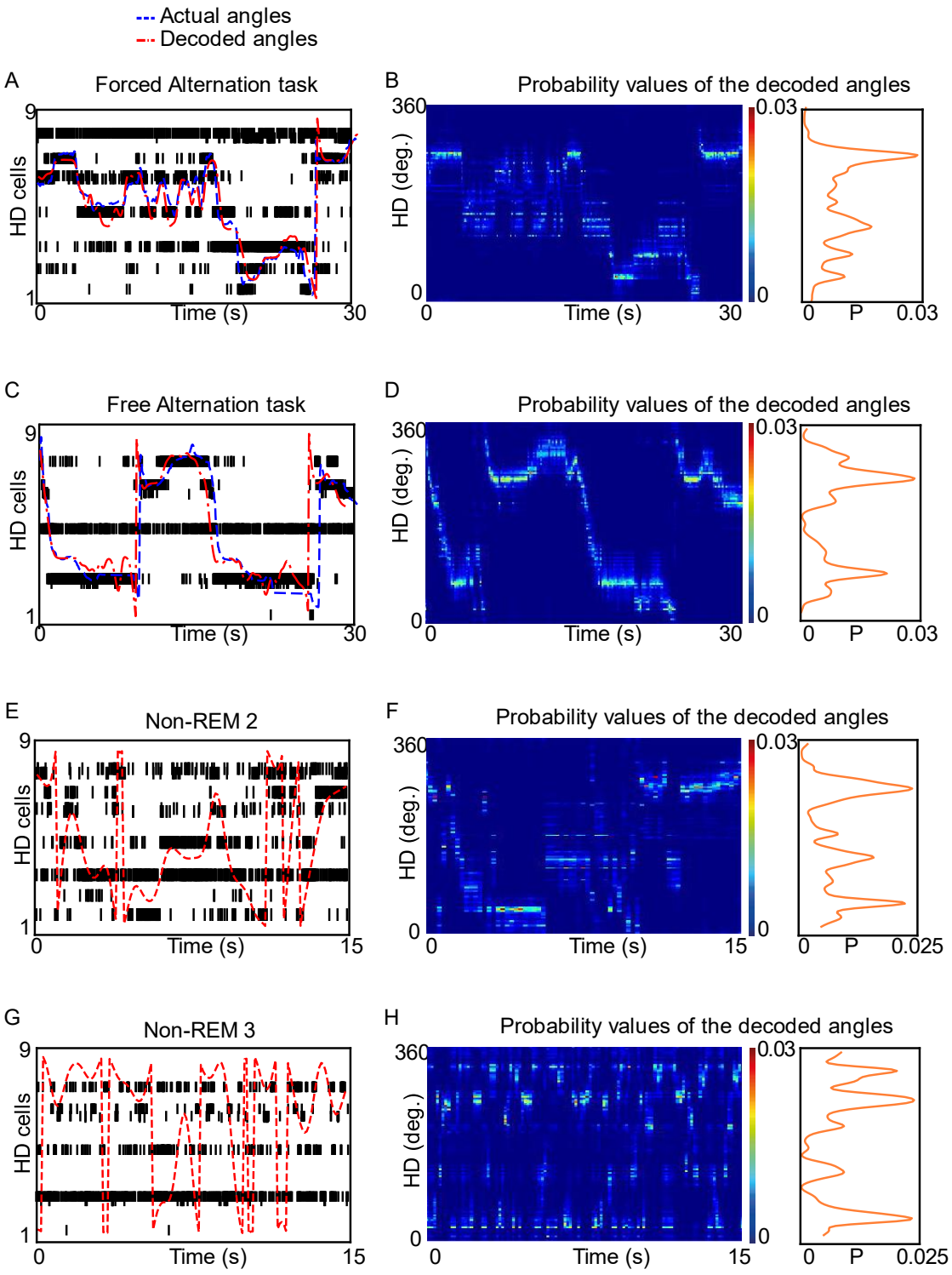

Figure 15 Linear Decoding of Head Direction signal. A) Left panel, spiking activity from head direction (HD) cell ensembles during the forced alternation task, and **B)** during the free alternation task. It shows both the actual (blue line) and the decoded (red line) head directions. **C and D)** Spiking activity during non-REM sleep 2 and 3. Middle panel, heatmap of the probability values for the decoded head direction angles throughout periods of wakefulness and non-REM sleep. Right panel, sum of probabilities of each angular direction.

6.5 The head direction attractor within the Anterodorsal Nucleus maintains its functional integrity during non-REM sleep.

To further investigate the stability of the head direction system's internal representation during wakefulness and sleep, we utilized the Isomap projection as an additional decoding method. This method allowed us to reduce the complex, high-dimensional activity patterns of the HD cell ensemble into a more interpretable two-dimensional space. By doing so, we could visually capture and analyze the continuity and changes in the HD system's internal structure during different states of consciousness. We computed the isomap projection of the HD cell population's activity throughout the execution of both tasks as well as during the non-REM sleep phases 2 and 3(Figure 17 A and B). In these projections, each point corresponds to the activity state of HD cells at distinct time bins, collectively forming a one-dimensional ring. The colour of each point reflects the orientation of the animal's head at the given time. Figure 17 C and D shows the angular direction's reconstruction.

We observed a consistent ring-like configuration in the HD system, consistent with the concept of a ring attractor model. This observation features the one-dimensional representation of HD under stable conditions. Remarkably, this architectural ring form was unaltered when comparing tasks of varying cognitive demands, from the less challenging forced alternation to the more demanding free alternation task. Additionally, the stability of the ring attractor persisted through various sleep stages, demonstrating a durable and persistent framework for spatial orientation that transcends task complexity and states of consciousness.

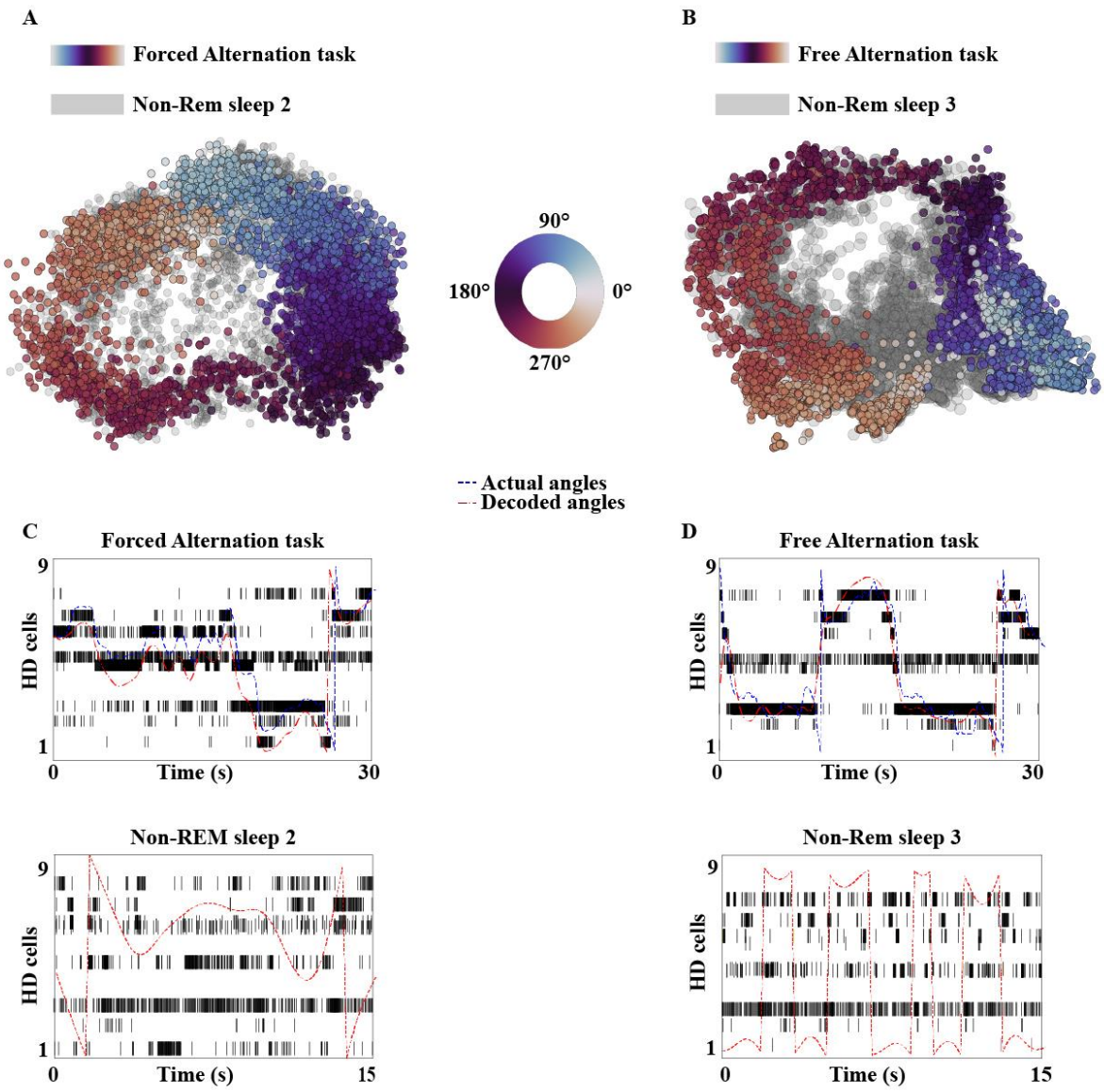

Figure 16 The head direction attractor network. A and B) Isomap projections show the activity of the head direction (HD) cell population during both tasks and during non-REM sleep 2 and 3, left and right, respectively. Each dot represents the HD cell activity at specific times, and when arranged in sequence, they create a one-dimensional ring. The color of each dot indicates the direction the animal's head is facing at that moment. C) Top, raster plot of the head direction (HD) cell ensembles activity during the forced alternation task, and D) during the free alternation task, showing both the actual (blue line) and the decoded (red line) head directions. Bottom, Spiking activity during subsequent non-REM sleep 2 and 3 showing decoded HD signal (red line).

6.6 Preferential Revisitation of Y-Maze Directions by Head Direction Signal During Non-REM Sleep Following Spatial Experience

After computing the actual uniform angle distributions (Figure 18 A and B, left panel) and the decoded probabilities during both tasks and their subsequent sleep session (Figure 18 A, B, right panel, and C, D), an interesting pattern emerged. The decoded angles demonstrated a non-uniform distribution, prompting a closer investigation into the particular aspects of spatial experience that are encoded and subsequently reactivated during sleep episodes. Intriguingly, it was found that six angles exhibited the highest probability values during non-REM sleep, which strikingly corresponded to the six actual angular directions of the maze (Figure 18 E).

Despite the higher cognitive demand associated with the free alternation task compared to the forced alternation task, this disparity did not significantly influence the representation of the decoded angles during subsequent non-REM sleep periods. This observation is corroborated by the lack of significant differences in the Bhattacharyya coefficients, underscoring a consistent encoding mechanism that transcends the cognitive complexity of the tasks (Figure 18 F). This finding suggests that the HD signal during non-REM sleep no longer corresponds to a continuous attractor. In the continuous attractor model the neural representation of head direction is stable across a continuum of all possible orientations, without preference for any specific direction. On the contrary, our results suggest that the HD signal during non-REM sleep selectively visits specific angles that are related to the task, indicating a preference or bias toward certain directions.

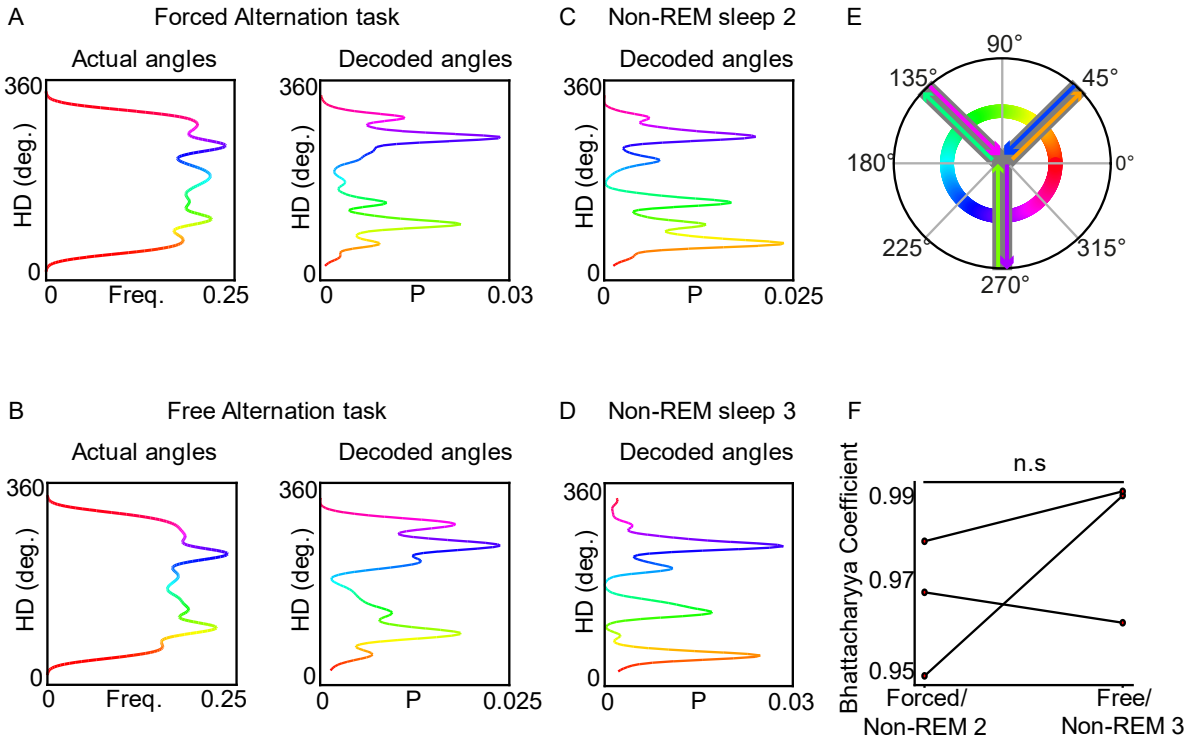

Figure 17 Y-Maze Patterns and Head Direction in Non-REM Sleep Post-Spatial Experience. A) Left, Frequency distribution of actual uniform angles during forced and **B)** free alternation tasks. Right, distribution of probability values of the decoded head direction signal during the corresponding task. **C)** Distribution of probability values of the decoded angular direction during non-REM sleep 2 and **D)** Non-REM sleep 3. **E)** Angular directions with higher probability values. **F)** Bhattacharyya coefficient of decoded angular distributions between forced alternation task and non-REM sleep 2 and between free alternation task and Non-REM sleep 3.

7. Discussion

7.1 Neural Synchronization during Sleep: Exploring the Coordination of CA1 Place and ADn Head Direction Cells

Since O'Keefe & Dostrovsky's seminal 1971 discovery, the study of hippocampal place cells has significantly advanced our understanding of spatial cognition. These neurons, which activate within specific locations or 'place fields' (O'Keefe & Dostrovsky, 1971; Wilson & McNaughton, 1993), are integral to the 'cognitive map,' facilitating spatial navigation and memory. Complementing this neural representation of location, Head Direction (HD) cells respond to the animal's head orientation, independent of location, integrating sensory cues for directional guidance (Cullen & Taube, 2017; Taube et al., 1990a). Within this complex neural network, ADn emerges as a crucial hub, densely populated with HD cells. These cells are pivotal for encoding and relaying directional cues to brain regions engaged in spatial navigation, seamlessly linking the cognitive map with the directional context. The essential role of the ADn in spatial memory further emphasizes this connection, where damage to this area leads to significant impairments in spatial task performance, underscoring the interrelated functions of place and head direction cells in spatial cognition and memory formation (Aggleton & O'Mara, 2022).

Although the individual contributions of place cells and head direction cells to spatial navigation and memory are well established, the intriguing question of whether the activity of these distinct cell types is coordinated remains open. This coordination is crucial to understand how the brain integrates spatial location with directional orientation to form a coherent representation of the environment. In 1995, Knierim et al, identified the strong coupling between hippocampal place cells and thalamic head direction cells, showing their coordinated response to environmental cues based on the rats' learned cue stability (Knierim

et al., 1995). This seminal work highlighted the intricate interplay between these neural systems in spatial navigation.

The precise dynamics between the hippocampal and thalamic systems—whether one drives the other or if they mutually influence each other—remain unclear. Additionally, the extent to which the observed coupling persists across various brain states, including sleep, prompts further investigation. This context sets the stage for the primary aim of our study, which is to explore the interaction and coordination between ADn-HD cells and CA1 place cells during non-REM sleep. Our focus is on understanding how their synchronized activity might influence the consolidation of spatial memories. Utilizing implanted high-density silicon probes, we tracked the activities of these cells across different states: wakefulness, engagement in tasks on a Y-maze, and during non-REM sleep sessions.

Notably, we observed that ADn-HD cells and CA1 place cells exhibited continuous activity throughout sleep, with a pattern of CA1 firing rates increasing 50-100ms after ADn spikes, highlighting a significant level of interplay between the two cell groups that might underpin the mechanisms of memory consolidation during sleep.

Contrary to our initial hypothesis, the coordination between ADn and CA1 during non-REM sleep was unaffected by the complexity of prior spatial learning tasks. This finding reveals a robust and uniform pattern of interaction where the activity within the ADn consistently influences, or drives, the responses observed in the CA1 region throughout sleep. This phenomenon occurs irrespective of the demands of the spatial tasks previously encountered, suggesting a fundamental and inherent mechanism of neural interaction that operates independently of the cognitive load imposed by prior experiences. This resilience of the ADn-CA1 coordination points towards an underlying neural architecture designed for consistency, potentially serving as a foundational process for the consolidation of spatial

memories. It underscores the capacity of the brain's spatial navigation system to maintain essential functional relationships, even in the face of varying cognitive challenges, thereby ensuring the stability of spatial memory encoding and retrieval processes across different states of consciousness.

7.2 Differential Reactivation of Thalamic and Hippocampal Neurons in Non-REM Sleep

Hippocampal replay, marked by the rapid reactivation of place cell sequences from previous exploration, during REM and non-REM sleep, plays a key role in memory consolidation (Lee & Wilson, 2002; Louie & Wilson, 2001; Skaggs & McNaughton, 1996; Wilson & McNaughton, 1994). This phenomenon extends to awake states during various behaviors, underlining its importance across cognitive functions (Diba & Buzsáki, 2007; Foster & Wilson, 2006).

Building on our previous discussion, ADn-HD cells and CA1 place cells exhibit synchronized rotations in response to visual cues during wakefulness (Knierim et al., 1995). Moreover, we observed a distinct pattern where ADn activity precedes CA1 responses during non-REM sleep. This consistent synchronization between head direction and hippocampal place cells across wakefulness and sleep phases indicates the potential for head direction cells to replay alongside hippocampal place cells. Although the coordinated replay between ADn-HD cells and hippocampal place cells has not been tested previously, Brandon et al. in 2012 conducted recordings of head direction and place cell ensembles in the postsubiculum during sleep before and after running on a circular track. Their findings revealed that during REM sleep, head direction cells did not replay activity patterns seen during waking periods of circular track running. Furthermore, postsubiculum spiking activity during hippocampal SWR events demonstrated that head direction cells remain inactive during these ripples (Brandon et

al., 2012). While this finding shows no coordinated replay between head direction cells and place cells in the postsubiculum during REM sleep and SWR, the possibility of synchronized reactivation between ADn-HD cells and CA1 place cells during non-REM sleep remains unexplored.

The second goal of this study aimed to delineate the reactivation patterns of CA1 place cells in the hippocampus and ADn-HD cells during non-REM sleep, thereby shedding light on the neural replay processes integral to spatial memory formation. To this end, we employed explained variance (EV) to explore neuronal reactivation during non-REM sleep, contrasting it with reversed explained variance (REV) to establish a baseline (Kudrimoti et al., 1999; Pennartz et al., 2004) . Consistent with our predictions, there was an absence of CA1 place cells reactivation during the sleep sessions following both tasks. The lack of CA1 place cell reactivation aligns with the theory that the hippocampus plays a key role in early stages of learning about new environments (Morris et al., 1982). As memories transition from being hippocampus-dependent and the gradually transferred to neocortical areas, the need for reactivation of specific place cells diminishes once the spatial information is consolidated or deemed familiar (Kudrimoti et al., 1999; Nádasdy et al., 1999; Wilson & McNaughton, 1994). The no significant reactivation might be attributed to the familiar environment of the Y maze alternation task, in which the mice were considerably trained for days. This extensive training likely led to a consolidation of spatial memories, reducing the need for reactivation in a well-known context. In line with our predictions, we observed a significant synchronized reactivation of ADn-HD cells and CA1 place cells only after the demanding free alternation task. In this context, the modulation of slow oscillations emerges as a potential mechanism driving the observed coordinated reactivation between thalamic and hippocampal cells. During non-REM sleep, slow-wave brain activity is characterized by slow oscillations (0.2–1 Hz). This activity alternates between periods of enhanced (Up states) and reduce activity

(Down states) (Steriade et al., 1993, 2001). These oscillations, which extend across the cortex, play a crucial role in memory consolidation and the enhancement of synaptic connections (Wei et al., 2016). The interplay between these two states might provide a structured temporal framework that may facilitate the reactivation of neuronal activity patterns (Malerba et al., 2014), including those from the hippocampus and ADn. Moreover, ADn serves as a central point for spreading slow oscillations, suggesting that HD cells might play a key role in coordinating neuronal activity within the limbic system, encompassing areas like the hippocampus, during NREM sleep (Gent et al., 2018) .

Intriguingly, something we were not expecting, we observed a robust reactivation of ADn-HD cell ensembles exclusively following the free alternation task during non-REM sleep 3, highlighting a task-specific reactivation pattern, but no reactivation in the sleep session after the less demanding forced alternation task. This unveiled a unique reactivation pattern tied to the complexity of the task, yet no such reactivation was observed during the sleep session after the more straightforward forced alternation task.

The free alternation task, which allows for autonomous decision-making and is inherently associated with emotional outcomes (reward or absence thereof), seems to engage the neural circuits more profoundly than the forced alternation task. This deeper engagement might be due to the combined cognitive load and emotional investment required in making choices and experiencing their consequences, which could lead to a more significant consolidation effort during sleep. The absence of reactivation following the forced alternation task, which involves less cognitive and emotional engagement due to its predictable nature and lack of choice, implies that the level of task complexity and emotional involvement plays a crucial role in determining which experiences are prioritized for reactivation and consolidation during sleep.

This finding underscores the intricate relationship between the nature of a task, its emotional impact, and the subsequent neural processing that occurs during sleep. It suggests that experiences with higher cognitive demands and emotional stakes are more likely to trigger reactivation in the ADn-HD cells, pointing to a selective consolidation process that may prioritize emotionally salient and cognitively challenging experiences. This selectivity could be an adaptive mechanism allowing the brain to focus its consolidative efforts on experiences that are more critical for adaptive behavior and learning.

7.3 Decoding Spatial Stability: Unveiling Neural Consistency Across Wakefulness and Non-REM Sleep.

Our third goal focused on uncovering what ADn-HD cells reactivate during non-REM sleep. We achieved this by reconstructing head direction, which allowed us to assess the possibility of replaying specific movement paths or orientation trajectories during non-REM sleep phases, thereby enhancing our grasp of the neural encoding and consolidation of spatial memories (Zheng et al., 2021). Anchoring this exploration was the hypothesis that the head-direction signal during non-REM sleep would selectively engage with components of the spatial memory task, suggesting a focused retrieval and reinforcement of task-relevant spatial information. To achieve this, we employed both Bayesian and linear decoding techniques to uncover the distribution of decoded angles during non-REM sleep after both tasks. This strategy showcased the brain's capability to maintain spatial representations across different states (Asumbisa et al., 2022; Viejo & Peyrache, 2020). Notably, this dual-method approach led to a pivotal discovery: a non-uniform distribution of decoded head direction angles during non-REM sleep, particularly aligning with Y-maze directional preferences following spatial tasks. Remarkably, six specific angles were preferentially revisited during non-REM sleep, matching the maze's orientations. This pattern was consistent despite the varied cognitive

demands of the tasks, suggesting a fundamental encoding mechanism within the head direction signal that remains stable across different states of consciousness and task complexities. These findings highlight the robustness of spatial encoding and memory consolidation processes during sleep.

It has been reported that after navigating a two-dimensional space, hippocampal CA1 cells replayed sequences are not confined to linear or previously traversed paths but exhibit a random nature (Stella et al., 2019), suggesting a complex and less predictable pattern of memory replay. However, our findings indicate that this may not be the case for ADn-HD cells, the decoded head direction angles during non-REM sleep, particularly aligning with Y-maze directional preferences following both spatial tasks. Notably, six specific angles were preferentially revisited during sleep, matching the maze's orientations. Whether the directions of the replayed trajectories, from start to end points, or the initial direction of the replayed trajectories correspond to the direction encoded by the ADn. The disparity in replay between CA1 and ADn-HD cells may stem from their distinct roles and encoding strategies. CA1 cells, known for their involvement in spatial and episodic memory (Burgess, 2002; Knierim et al., 2006; D. M. Smith & Mizumori, 2006; Sugar & Moser, 2019), might exhibit more stochastic replays to integrate diverse experiences, enhancing cognitive flexibility. In contrast, ADn-HD cells, crucial for maintaining directional orientation (Peyrache et al., 2019), show a more consistent replay pattern, likely reflecting their role in stabilizing spatial navigation cues. This difference underscores the brain's multifaceted approach to memory consolidation, balancing the need for flexibility and stability in spatial representations. Additionally, Viejo and Peyrache's reported that HD cells align with specific directions during hippocampal SWRs in non-REM sleep, suggests a guiding role for these cells in memory replay (Viejo & Peyrache, 2020). This complements our observations of six specific angles being revisited during sleep, which resonate with the maze's configurations. Together, these studies underscore the

coordinated role of HD cells in directing the hippocampus's replay of spatial memories, enriching our understanding of memory consolidation during sleep.

7.4 Preservation of the Ring Attractor Model in ADn During Non-REM Sleep

The maintenance of a functional structure by the head direction system within the ADn during non-REM sleep extends the current understanding of neural mechanisms underlying spatial orientation (Peyrache et al., 2015). The application of Isomap projections to simplify the complex activity of the HD cell ensemble into a low-dimensional, interpretable format has revealed a persistent ring-like configuration across various task complexities and sleep stages (Chaudhuri et al., 2019; Knierim & Zhang, 2012; Skaggs et al., 1995). This configuration is emblematic of a ring attractor model, suggesting an intrinsic, stable representation of spatial orientation that transcends the immediate requirements of cognitive tasks and the state of consciousness.

Utilizing Isomap projection, we observed a consistent organization within the HD system across wakefulness and non-REM sleep states, indicating an invariant structural integrity that plays a pivotal role in consolidating spatial memory, potentially by reinforcing the pathways responsible for encoding directional information. This method allowed us to decode the head direction signal across different brain states, further underscoring the system's capacity to maintain an internal, coherent directional orientation without reliance on external cues—a capability crucial for effective navigation and spatial comprehension upon awakening (Peyrache et al., 2015). The unwavering performance of the HD system across various sleep stages underscores the significant contribution of non-REM sleep to memory processes, particularly in the stabilization and refinement of spatial orientation neural codes. These insights reveal that the brain's systems for spatial orientation and memory remain active

and functional during both wakefulness and sleep, undertaking essential organizational and consolidation tasks. This ongoing activity during non-REM sleep is instrumental in weaving together new and existing spatial information, thereby bolstering the adaptability and resilience of spatial memory.

7.5 Future research

Our findings contribute to the understanding of neural coordination between hippocampal CA1 place cells and thalamic ADn head direction cells during sleep, emphasizing their role in memory consolidation. The ADn-HD consistent precedence over CA1 place cell responses, irrespective of sleep sessions or task complexity, hints at a fundamental spatial memory processing mechanism. Future research avenues include deeper exploration of ADn and CA1 interactions to examine the flow of information during sleep, and the investigation of other interconnected regions like the medial entorhinal cortex to further understand spatial memory consolidation network dynamics. Another area of interest is the differential impact of sleep states on neural coordination and memory processing, particularly the distinct roles of REM and non-REM sleep.

Adding to this research landscape is the unexplored domain of thalamic reactivation during sleep, particularly the reactivation of ADn-HD cells in offline states observed in this study. Furthermore, exploring the reactivation of ADn-HD cells during SWRs is paramount for several key reasons. First, SWRs are critical periods of heightened neural activity in the hippocampus, associated with the replay of previously acquired spatial information, which is fundamental for memory consolidation (Buzsáki, 2015). The involvement of ADn-HD cells, known for encoding the brain's internal compass, during these ripples could elucidate how directional cues are integrated into spatial memories during these pivotal memory

consolidation windows. Secondly, understanding the reactivation of ADn-HD cells during SWRs could reveal novel insights into how the brain navigational system operates at a network level, particularly in synthesizing spatial and directional information. This is crucial for comprehending how memories of environments and contexts are not only formed but also how they are stabilized and stored for long-term recall. Furthermore, the investigation into ADn-HD reactivation during SWRs could have significant implications for developing therapeutic strategies for memory-related disorders. Disruptions in SWR activity and hippocampal-thalamic interactions have been implicated in conditions like Alzheimer's disease and epilepsy (Aggleton et al., 2016; Dinkelacker et al., 2015; Jones et al., 2019; Zhen et al., 2021). Thus, a deeper understanding of these processes could pave the way for novel interventions targeting the restoration or enhancement of memory consolidation mechanisms. Lastly, this line of inquiry could contribute to the broader field of computational neuroscience by providing empirical data to refine existing models of hippocampal function and to develop more accurate simulations of neural networks involved in memory processes. This, in turn, can advance our theoretical understanding of the brain memory systems and inform the design of artificial intelligence systems that mimic human learning and memory consolidation processes.

In our study, the distinction between the free and forced alternation tasks in the Y-maze extends beyond cognitive demand to encompass the inherent emotional content of each task. Unlike the forced alternation task, where the path of the animal is predetermined, the free alternation task allows the animal to choose its path, leading to an outcome that is either rewarding, through the delivery of an appetitive stimulus, or effectively punitive, through the absence of an expected reward. This element of choice endows the task with a higher emotional significance as the outcomes directly correlate with the decision of the animal,

potentially intensifying the emotional impact of those experiences (Brosch et al., 2013; LeDoux, 1994) .

The differential emotional valence attached to the free alternation task outcomes could significantly influence the reactivation patterns observed in ADn-HD cells during sleep. The presence of a reward or its absence not only serves as a spatial marker but also carries emotional weight, potentially enhancing the salience of the memory trace formed during the task. This salience could lead to a more pronounced or differentiated reactivation during sleep, reflecting the integration of both spatial orientation and emotional experience (Laventure & Benchenane, 2020).

8. Conclusions

In this study, we delved into the complex interactions between hippocampal CA1 place cells and ADn-HD cells during non-REM sleep to understand their coordinated influence on spatial memory consolidation. A key finding was the coordinated reactivation of ADn-HD cell and CA1 place cell ensembles during non-REM sleep, and particularly the pronounced reactivation of ADn cells, notably after the free alternation task, highlighting a task-specific reactivation pattern. Moreover, the non-random nature of the decoded HD signal, revisiting the six possible Y-maze trajectories during non-REM sleep, points to a selective consolidation process prioritizing directional information.

This research revealed that the ADn-HD signal not only undergoes selective reactivation but also drives the activity of CA1 place cells, indicating a synchronized effort in memory consolidation. Importantly, this coordinated activity between ADn-HD and CA1 place cells remained consistent, independent of the sleep session or the preceding task

complexity, suggesting a fundamental and stable neural mechanism pivotal for spatial orientation and memory across various cognitive demands and states of consciousness.

In summary, our findings reveal that the collective activity of thalamic HD cells and CA1 place cells is altered by learning experiences, a change that is mirrored in the patterns of activity during subsequent sleep. Despite the preservation of ADn-HD tuning across various tasks, the results indicate that the encoding of learning-specific information occurs independently of the HD signal. Although ADn activity consistently precedes CA1 spiking, it appears that learning enhances the synchrony between anterior thalamic cells and hippocampal neurons activated during wakeful experiences. Our observations suggest that spatial learning can reshape the organization of the HD system, which is traditionally thought to be controlled by low-dimensional attractor dynamics. However, the specific mechanism by which learning modifies the organization of the HD system remains unknown.

9. References

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