QUERYING HIPPOCAMPAL REPLAY WITH SUBCORTICAL INPUTS

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Querying hippocampal replay with subcortical inputs.

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Abstract

During sleep, the hippocampus recapitulates neuronal patterns corresponding to behavioral trajectories during previous experiences. This hippocampal replay supports the formation of long-term memories. Yet, whether replay originates within the hippocampal circuitry or is initiated by extrahippocampal inputs is unknown. Here, I review recent findings regarding the organization of neuronal activity upstream to the hippocampus, in the head-direction (HD) and grid cell networks, and its relationship to replay. I argue that hippocampal activity at the onset of replay is under the influence of signals from primary spatial areas. In turn, hippocampal replay resets the HD network activity to select a new direction for the next replay event. This reciprocal interaction between the HD network and the hippocampus may be essential in grounding meaning to hippocampal activity, specifically by training decoders of hippocampal sequences. Neuronal dynamics in thalamo-hippocampal loops may thus be instrumental for memory processes during sleep.

Introduction

The role of the hippocampus and its associated structures in the formation of long-term explicit memories (of facts and events) has long been established [1–4]. Interestingly, the same circuits that are involved in memory are involved in representing the present location and the ability to navigate [5]. The hippocampus is the seat of a spatial cognitive map, as evidenced by the presence of "place cells", which fire when the animal is in a specific location in the environment [6] and allow it to navigate [7]. What is the relationship between navigation and long-term memory formation? In a seminal paper, David Marr wrote [8]:

"*The neocortex may be regarded as a structure which classifies the information presented to it. […] At a given moment, there will exist in an animal's brain information whose expression is now as sophisticated as the animal either requires or can provide.* ***Further classification of the information may be carried out later*** *but, at that moment, the animal needs simply to be able to store it in its present form*. [..] *the* ***Regio Entorhinalis*** *and the* ***Regio Presubicularis*** *prepare information from many different sources for its simple representation in the [hippocampus]*"

Prominent theories from Marr and followers posit a two-way dialogue between the hippocampus and the neocortex: encoding of neocortical states in the hippocampus during experience and spontaneous reactivation of hippocampal patterns during sleep [3,8,9], demonstrated by the observation that patterns of co-active place cells during navigation are replayed during subsequent sleep episodes [10,11]. Repetition of this activity would allow the neocortex to eventually store memories, even for episodes that have, by definition, happened only once. However, the mechanisms that determine the content of hippocampal replay remain unknown. Is the content governed entirely by intrahippocampal circuits and just decoded

by the same regions that encode information during wakefulness, namely the entorhinal cortex and the presubiculum, to use more modern terminology? Or is the hippocampus still influenced by its inputs while in this "disengaged" state? Here, I review the sequence of physiological events that support replay and present a hypothesis that subcortical signals, in particular those from a network of circuits responsible for processing head direction (HD), constrain hippocampal ensembles during sleep into activity patterns corresponding to specific travel directions. Rather than a simple prompt for replay-to-be-consolidated, I propose that the HD signal is a key component in a query-training process by which the content of hippocampal activity is grounded through its correspondence to primary spatial inputs.

Thalamocortical dynamics during NREM sleep and their relationship with learning and memory

Since the seminal discovery of memory replay during non-rapid eye movement (NREM) sleep[10,11], efforts have been deployed to identify its neuronal and circuit basis. In the hippocampus, network activity during NREM is dominated by sharp wave-ripples (SWRs), high frequency (120-200 Hz) transient oscillations lasting about 100 ms [12]. SWRs are associated with the activation of neuronal sequences similar to those seen during previous experiences [11,12], which are instrumental in memory formation [13–15].

Beyond the hippocampus, NREM sleep is characterized by a dramatic shift in neuronal dynamics throughout the forebrain. Around the same time as the discovery of hippocampal replay, it was shown that neurons in thalamocortical networks fluctuate between activated UP and inactivated DOWN states, forming at the population level the so-called slow oscillation in the local field potentials (LFPs) [16]. Replay events are not independent from this cortical activity. The occurrence of SWRs is influenced by the phase of the slow oscillation [17–19], with a marked decrease in SWR occurrence during thalamocortical DOWN states [19,20]. In turn, it was recently suggested that SWRs influence thalamocortical dynamics by resetting the phase of the slow oscillation [21].

DOWN-UP state fluctuations tend to be synchronous over large cortical networks, although localized fluctuations are often observed. The anterior thalamus, in particular the anterodorsal nucleus (ADN) of the thalamus, plays an essential role in synchronizing UP states in the posterior and medial cortex [22]. So far, the influence of thalamocortical inputs on hippocampal activity, especially on SWRs during NREM, have been mainly investigated in terms of overall population firing and LFP. It is only recently that the information conveyed by spontaneous activity upstream of the hippocampus has been decoded during NREM sleep.

Attractor dynamics upstream of the hippocampus during wake and sleep

In order to make use of a map, one needs a compass to self-orient. In the brain, this is in the form of HD neurons, which each fire for a specific direction of the head in the horizontal plane [23] (Fig. 1A). While other sensory systems convey signals that are essentially encoded in egocentric coordinates (e.g. "I hear/see/smell something on my right"), the HD signal is an allocentric signal which is available even in the absence of any other sensory inputs. The HD signal originates in the brainstem and reaches the cortex

via the ADN. While the functional neuroanatomy of the HD circuit has been the subject of a large body of experimental work (see refs [24] for review), this review will focus on the thalamocortical component of the HD system, linking ADN with its main cortical target - the post-subiculum (PoSub, or dorsal presubiculum).

The crucial property of the HD system is to represent a single direction at any given time. To ensure reliable signal transmission independent of the availability of particular sensory modalities (e.g. in light versus in darkness), a direction is encoded by a unique subset of similarly tuned HD neurons (Fig. 1B). From a computational perspective, the HD system is a canonical example of an attractor network [25] whereby internal circuits constrain neuronal population activity into a low dimensional subspace of possible states. For the HD system, these states are continuously distributed along a functional ring (Fig. 1C), which can be identified by projecting multi-neuronal data onto a low dimensional map using dimensionality reduction and machine learning techniques [20,26] (Fig. 1C).

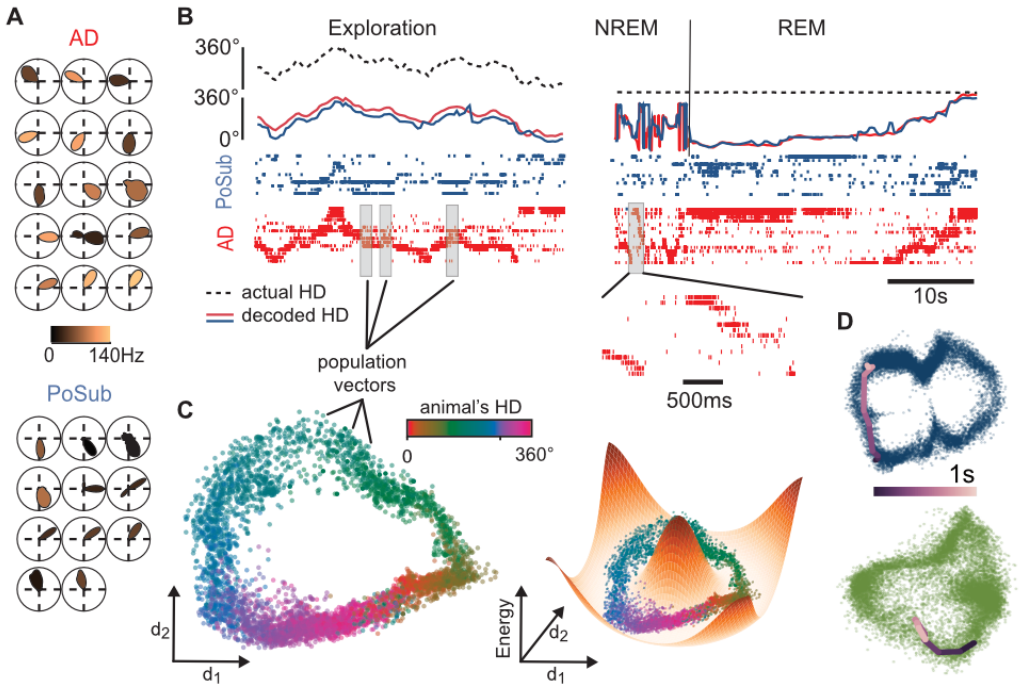

Figure 1. Attractor dynamics in the HD network.

A) Tuning curves (in polar plots) of simultaneously recorded HD Cells in the ADN-PoSub network. Color displays peak firing rates.

B) HD cell population activity across brain states (exploration, NREM and REM, from left to right). *Top*, actual animal's HD (dotted line) and Bayesian reconstruction from ADN and PoSub HD cell population in red and blue, respectively. Bottom, raster plots of HD cell activity, each row showing the spiking activity of an individual cell. HD cells are sorted by preferred direction separately for each structure.

C) *Left*, 2-dimensional projection of population activity during wakefulness. Each dot is the projection of a population vector, colored by the instantaneous animal's HD. Population vectors for similar animal's HD are close in projection space. *Right*, the organization of population activity along a functional ring may correspond to states of low energy in the system, as predicted from a ring attractor network.

D) Two-dimensional projection of population activity during wakefulness (top, blue) and REM (bottom, green). Example trajectories of HD cell population activity lasting one second during these two brain states are overlaid.

A,B adapted from ref [27]. C,D adapted from refs [20,26]

A key feature of an attractor network is that population activity maintains its internal organization irrespective of brain state and in the absence of sensory input. This state-independence is particularly striking during REM sleep, when the patterns of electrical activity and the levels of neuromodulation are similar to wakefulness [28]. In fact, HD cell population activity during REM sleep is, at first sight, virtually indistinguishable from wakefulness, despite drifting around the ring in an apparently random fashion (Fig. 1D).

The medial entorhinal cortex (MEC) sits at a unique position between the head direction system and the hippocampus. It is one of the main output structures of the PoSub, and a majority of MEC neurons are modulated by the animal's HD [29]. It is also the main input and output structure of the hippocampus in the cortex, and grid cells in the MEC show regular firing in space such that their firing fields tessellate the environment with an hexagonal pattern [30]. The HD signal is certainly an essential input for the emergence of grid cells [31]. A large class of computational models of grid cell generation suggest they are endowed with the same kind of attractor dynamics as HD cells [32–34]. As predicted, the organization of grid cell population activity is also preserved during REM sleep [35–37]. These observations provide evidence for attractor dynamics within the grid cell network.

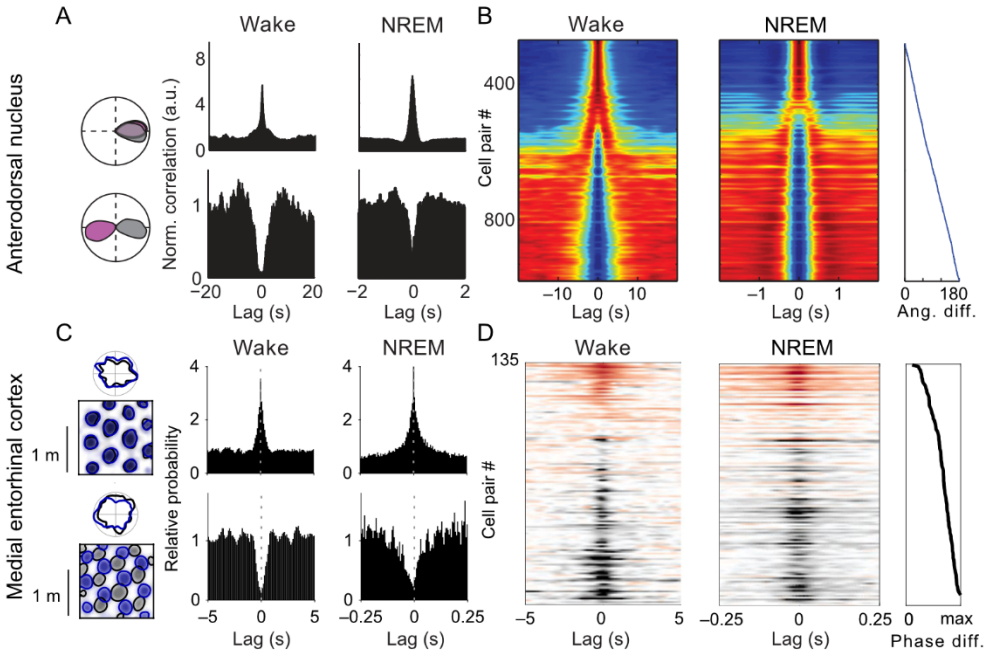

Figure 2. **Preserved coordinnation at fast temporal scale in the HD-grid network during NREM.**
A) Left, tuning curves of two HD cell pairs firing for the same (top) and opposite (bottom) directions. Right, spike train cross-correlograms of the same pairs during wakefulness and NREM. Note the change in time axis.
B) Cross-correlograms of multiple HD cell pairs (same as A but color-coded from blue to red showing minimal to maximal correlation values for each pair, respectively). Pairs are sorted by angular offset of preferred direction for each pair (right).
C-D) Same as A-B for pairs of simultaneously recorded grid cells of similar grid spacing (note that spike train coordination are computed with generalized linear models, not directly cross-correlograms). Grid cells may be in phase (C, top) and anti-phase (C, bottom). Cell pairs in D are sorted by phase difference and coordination is color coded from dark to red, showing minimal to maximal co-activation probability, respectively.
A-B adapted from ref [27]; C-D adapted with permission from ref [35].

Attractor dynamics in the HD-grid cell network, as evidenced by the high similarity between activity patterns during wakefulness and REM sleep, raises the possibility that neuronal coordination must be

preserved during NREM sleep as well. At the population level, HD cell activity seems coordinated but drifts at a much faster pace than during wake/REM (Fig. 1B). Spike train cross-correlograms of HD cell pairs show that while the magnitude of zero-lag correlation between wake and NREM is preserved, they appear temporally compressed during NREM (Fig. 2A). Hence, the timescale at which the system remains in each position is an order of magnitude shorter than during wakefulness and REM sleep. The same observations were made for grid cells [35,37], which preserve their co-activation patterns while drifting at fast speed during NREM (Fig. 2B). This temporal compression of HD and grid neuronal patterns echoes the compression of neuronal replay events in the hippocampus [11,38].

Querying the hippocampus with a stable HD signal during SWRs.

During NREM sleep, HD cell activity drifts at angular velocities that are, on average, 5 to 10 times higher than during wakefulness and REM sleep (i.e. active states) yet, this distribution is broad with velocities ranging from stable direction to fast sweeps at angular speed never observed during exploration[27,39]. Interestingly, this echoes animals' natural movements, in which bouts of locomotion associated with fairly stable head direction alternate with pauses during which animals perform head scans [40,41]. Could it be possible that a similar relationship exists between virtual head movement and spontaneous replay of trajectories in the hippocampus during NREM? Furthermore, in contrast to active states during which HD cell population maintains high activity level, HD cell population often visits "forbidden" states of the attractor during NREM that is states that lie inside the topological ring (e.g. closer to the center) and are virtually never visited during wave and REM. This results from fluctuation in population activity, which will be here referred to as the "gain" of the network. Last, the network gain spans all possible magnitudes from active state levels during UP states to global population silence during DOWN states [26]. As the ADN is a key node in the synchronization of the slow oscillation (see above), one could expect a tight relationship between ADN gain levels and hippocampal activity.

Simultaneous recordings of ADN-HD cell populations and LFP in CA1 show that ADN-HD cells reliably fire immediately before SWRs (Fig. 3A). This indicates that the gain of ADN-HD cells increases prior to SWRs (to note, this gain modulation is independent of DOWN-UP fluctuations as SWRs can occur at any phase of the ADN UP state [20]). The ADN is the only anterior thalamic nucleus to show this homogeneous increase before SWRs [20], pointing to a specific role of this nucleus in coordinating activity across large cortical networks [22]. To decode the HD signal, HD cell population activity was projected onto a 2-dimensional subspace [20,26] (Fig. 3C) in which the radius and the angle from origin correspond to the gain and internal HD, respectively. Two key observations are made. First, as expected from single cell response, the HD cell population trajectories in this projection subspace reach the outer perimeter of the distribution immediately before SWRs, with gain levels corresponding to active states (Fig. 3D). Second, the ADN-HD signal is stabilized (as measured by the decrease in angular velocity), also before SWRs (Fig. 3E). This inverse relationship between drifting speed and gain in the ADN-HD network may not be specific to sleep as it was recently observed in foraging mice [42].

These results raise the intriguing possibility that the onset of hippocampal replay is influenced by subcortical inputs, in particular a stable and high-gain HD signal which is engaged immediately prior to SWRs. While the HD signal rotates rapidly during majority of NREM, replay of trajectories is associated

with a stable HD signal, not unlike HD during natural movement. Yet, replayed trajectories after exploration of an open field are not all necessarily linear [43]. The HD signal may thus perhaps constrain the overall direction of the replayed trajectories or perhaps just the starting direction.

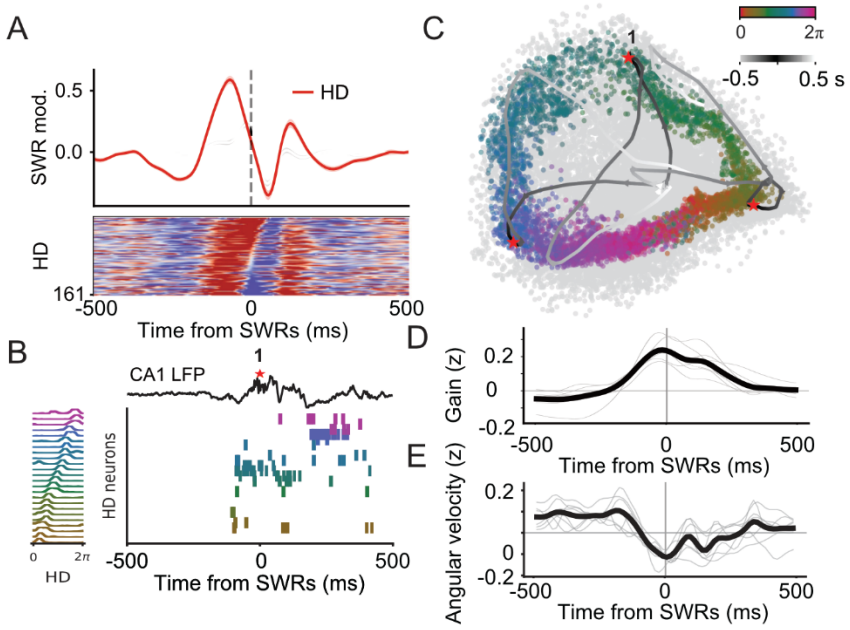

Figure 3. Increases gain and stabilization of the HD signal immediately before SWRs.
A) Normalized activation of individual ADN-HD cells relative to SWR times (bottom) and average (top).
B) Example ADN-HD cell population activity around the time of a SWR (indicated with an asterisk in the CA1 LFP trace, top). Cells are sorted relative to their preferred direction (tuning curves in cartesian plots shown in left).
C) ADH-HD cell population trajectories from -500 to 500ms around three example SWRs in 2-dimensional projection space. Projected activity in NREM (gray dots) is shown together with population activity during wakefulness (colored dots). The three asterisks indicate the time of three example SWRs with "1" indicating the one showing in B. Note that population activity reaches gain levels of wakefulness immediately before and during each SWR.
D) Average normalized gain of ADN-HD cells around SWRs (dark line). Each individual session is shown as thin gray line.
E) Same as D for angular velocity of the ADN-HD signal.
Adapted from ref [20]

Is the content of hippocampal replay dictated by its inputs?

The ADN-PoSub HD network does not contact the hippocampus directly, and the question remains if the MEC exhibits similar properties around SWRs which are passed on to the hippocampus. The MEC projects to the hippocampus from its superficial layers and, in turn, receives inputs from the hippocampus in its deep layers [44]. Hippocampal SWRs have a strong impact on its output structures [45], directly activating deep layers of retrohippocampal areas, including the MEC [45]. As grid cells are coordinated during NREM sleep, do they replay trajectories coherently with the hippocampus and is there a difference across layers?

Two studies performing simultaneous recordings in the CA1-MEC networks provided fundamental insights into this question. CA1 place cells and deep layer grid cells are reactivated coherently [46]. Grid cell replay tends to follow place cell replay, as expected from CA1 projections to the deep layers of the MEC [44] and

the delayed ripples observed in these layers [45]. In contrast, superficial layer grid cell replay events were largely independent of CA1 replay when considered from a pure spatial perspective (i.e. replay of spatial trajectories in the MEC) [47]. However, despite these observations, it is too premature to declare that hippocampal information content during replay is only dictated by intrahippocampal events. First, a majority of cells in MEC layer 3 – which project to CA1 - show directional tuning [29]. The correspondence between the activity of these MEC HD cells and CA1 replay is still unknown. Furthermore, it is possible that grid cells themselves provide directional input to the hippocampus independently of any specific (i.e. replayed) trajectory. This could be encoded by the drifting direction of grid cells, not necessarily related to the replay of specific neuronal patterns. Hence, considering the dynamics of ADN-HD cells around SWRs and the contribution of HD cell firing for MEC spatial representation [31,48], it is in fact quite likely that a directional signal linked to SWRs activity is present in the MEC, upstream the hippocampus.

Learning to read out hippocampal code during SWRs and formation of spatial memories.

One crucial question regarding hippocampal replay is how this code is read out by output structures to support memory consolidation. SWRs activate the deep layers of retrohippocampal areas, including the PoSub [45]. Information flow from these retrohippocampal areas to the neocortex certainly supports memory consolidation [49] but the exact nature of the processes at play are still a matter of debate. Yet, one can speculate on the role of CA1 inputs to the PoSub at times of SWRs and, more generally, the role of the HD signal in the consolidation of spatial memories. The PoSub is ideally situated to compare the direction represented by ADN-HD cells prior to SWRs with the direction of the replayed sequence in CA1. Under this scheme, the SWR-initializing head direction acts as a "query" to the hippocampal system, which produces a replay sequence in a specific direction on the hippocampal map, which is then decoded by the head direction system. Mismatch between the queried and decoded directions would lead to an adjustment of the network to optimize the decoder. In other words, this "query-training" process would support the training of a decoder reading out the directional tuning of CA1 ensembles, and alignment between the head direction signal and hippocampal maps so that internal spatial representations remain coherent (Fig. 4).

How might query-training support spatial memory formation, as well as alignment between the HD signal and hippocampal maps? A key might be found in the interaction between these spatial signals and visual input. Artificial deep learning networks have revealed a fundamental relationship between learning a mapping between visual inputs, position and head-direction and developing a flexible representation of an environment, independent of the viewpoint [50]. Vision exerts a strong influence on the orientation of the HD signal during exploration as animals are able to use proximal and distal cues to update their sense of direction [51–53]. Importantly, animals should be able to get oriented even from previously unvisited viewpoints in a familiar environment. Interestingly, hippocampal replay during sleep generates previously non-experienced trajectories in a given environment [43,54]. One possibility is thus that, through queries of unseen viewpoints, the query-training processes help the brain generalize to all possible viewpoints, allowing animals to form a viewpoint-independent spatial memory and efficiently navigate during future visits.

The query-training hypothesis is supported by an important detail regarding replay of grid cells in the deep layer of the MEC, which are often also modulated by animal's HD [55]. Interestingly, grid-place coherence is correlated with the directional tuning of deep layer grid cells [46], suggesting a tight relationship between place and HD signals during replay. Furthermore, the visual sensory cortex replays together with the hippocampus during sleep [56], as expected from a process learning to match viewpoint and visual inputs.

This prompts a novel question for spatial memory research: what is the physiological nature of the PoSub decoder (i.e. of hippocampal output) and its learning? The high coherence of the HD cell population in the ADN-PoSub network across environments and brain states [27,39,53] suggests that the activity in this thalamocortical network is rigidly organized and that the hippocampus can, at most, reorient the HD signal. "Online" learning can already take place during exploration. Hippocampal-PoSub synapses can be trained to match hippocampal activity patterns – from which head direction can be decoded by an ideal observer [57] – with the "labels" corresponding to PoSub states (i.e. a direction) during exploration. To note, the alignment of the internal HD signal with the external world is certainly independent of the hippocampus. During the visit of a novel environment, it takes several minutes for the HD signal to stabilize in the ADN-PoSub network [52]. As the same transient instability is observed in hippocampus-lesioned animals [58], this unstable period certainly corresponds to plasticity between the visual and HD systems and is independent of the hippocampus. Hence, plasticity within hippocampal-PoSub synapses would support learning of a decoder aligning hippocampal maps with the HD system but not aligning the HD system with the environment. As suggested above, "offline" learning may then take place during SWRs to align unexperienced spatial trajectories with the HD signal. The plasticity of this pathway remains to be investigated.

While it is still unclear if PoSub-HD cells are specifically activated by SWRs [39,59], ADN-HD cells are, in contrast, inhibited immediately after SWRs (Fig. 3A). This observation points to a reciprocal interaction between the HD system and the hippocampus, which may have further implications for spatial memory formation. But what are the circuits that support this post-SWRs inhibition in the ADN? In the thalamus, the main source of inhibition arises from the thalamic reticular nucleus (TRN), a layer of inhibitory neurons surrounding the thalamus that is reciprocally connected with many (but not all) thalamic nuclei [60,61]. In the anterior thalamus, ADN is the nucleus showing the strongest reciprocal connections with the TRN [53,62,63]. As in any thalamocortical networks, deep layer PoSub neurons send feedforward excitatory connections to the ADN [64] as well as collaterals within the thalamic reticular nucleus (TRN) [63]. These connections result in a strong hyperpolarization of ADN neurons when PoSub cells are activated [63]. Hence, SWR-activated PoSub neurons may lead to the inhibition of ADN neurons.

This post-SWRs activation of the TRN may have two meaningful consequences. First, TRN activation triggers spindles [65], oscillations that are believed to be associated with plasticity in thalamocortical networks [66]. In this case, plasticity during SWR-triggered spindles would support training of the place-to-HD decoder. It is possible that the CA1-PoSub-TRN pathway is also a key circuit supporting the coordination of SWR and spindles observed in the medial cortex [17,21]. Second, the inverse relationship between network gain and drifting speed in the ADN-HD cell population [20,42] suggests that SWRs lead to an indirect rebound in drifting speed and randomly fluctuations in the HD signal after SWRs. These fast drifts are observed in experimental data (Fig. 3B-C) and could potentially select a new direction at random before the next SWR occurs. In support of these two predictions, HD drifts are associated with increased power in the spindle band [26].

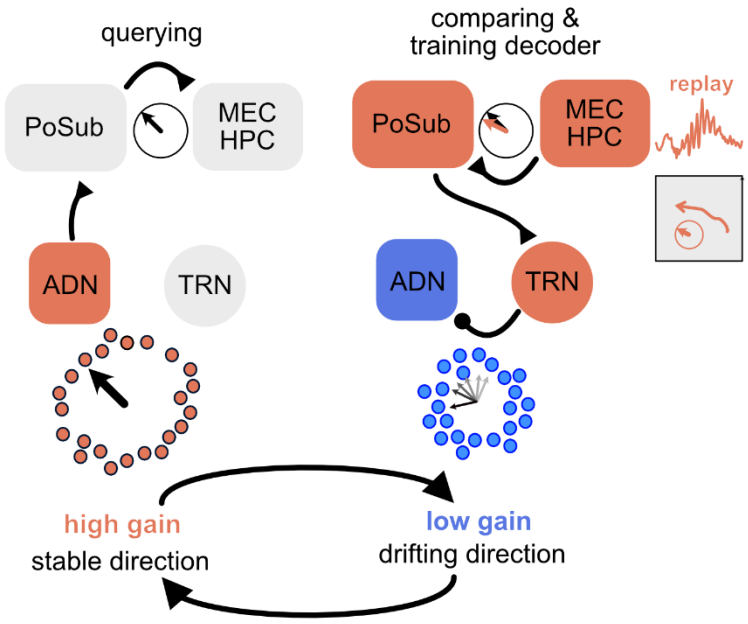

Figure 4. The querying-training hypothesis.

During NREM, ADN-HD cell population alternates between states of high and low activity gain, associated with stable and fast drifting directions, respectively (bottom). States of high gain influence downstream structures and may lead to the generation of SWRs in the hippocampus. At times of SWRs, the ADN would query the hippocampus with a specific direction (dark arrow in a circle, top left). During the SWR, a neuronal sequence replays a spatial trajectory (orange trajectory on a schematic square gray box, right), from which a direction can be decoded (orange arrow in a circle). The PoSub can then compare the queried and replayed directions to train a place-to-HD decoder of hippocampal sequences. This process would give meaning to hippocampal sequences and support the formation of long-term spatial memories. In turn, the activation of the PoSub leads to a feedforward inhibition of the ADN (through activation of the TRN), shifting the ADN-HD cell population in a state of low gain and fast drifting direction. Lines connecting structures show excitatory and inhibitory pathways with triangles and circles, respectively.

Conclusion and predictions

In summary, the thalamocortical loop composed of the ADN, PoSub, MEC and the hippocampus would play an essential role in memory formation. The "simple" representation (in David Marr's words) of animal's HD constitutes a key link between the external world and internal state that gives meaning to hippocampal neuronal sequences. Specifically, the PoSub would encode multimodal sensory inputs, especially vision and vestibular information, into a code for HD. In turn, it would decode animal's HD from hippocampal sequences and match it with the estimate provided by sensory evidence. During sleep, the training of this place-to-HD decoder would take place by first querying the hippocampus with a direction, selected by the subcortical HD network, and compare it with the direction decoded from the neuronal sequence that the hippocampus produces during SWRs. Following SWRs, feedforward inhibition of the ADN allows the system to select a new direction.

The formation of a mapping between spatial position, head direction, and visual inputs may constitute the basis of a spatial memory which, after sufficient training during exploration and sleep, may progressively become independent of the hippocampus. While the PoSub may be principally involved in

the decoding of the HD signal, other structures such as the retrosplenial cortex, which is involved in long-term spatial memories [67] and receive direct inputs from the ADN [68], may play a key role in mapping spatial location and visual inputs.

Several predictions can be made from the query-training hypothesis of sleep replay. As the visual system shows coordinated replay with the hippocampus [56], it would be interesting to see whether the visual system can also generate previously unvisited inputs during generative replay [54] and whether this generative signals are dependent on the PoSub and the retrosplenial cortex. Furthermore, while the hippocampus is not necessary for the establishment of a stable HD signal in a novel environment, hippocampus-lesioned animals may fail to get correctly oriented from a previously unvisited viewpoint. Finally, the synapses from the hippocampus to the PoSub should be plastic and blocking this plasticity should lead to a systematic mismatch in the PoSub between the HD signal before and during SWR. Further work will test these predictions *in vivo* and *in silico*.

The origin of this spontaneous activity in the HD network remains unclear. It can emerge in the generator circuit of the HD signal (i.e. in the mammillary bodies and dorsal tegmental nucleus [24]). As spontaneous activity during NREM seems to originate in the midline thalamus and relayed by the ADN [22], there is also a possibility that this activity emerges in the ADN-PoSub circuit independent of upstream activity. Furthermore, the HD signal is not the only information that may influence the content of hippocampal replay. As previously demonstrated, following the learning of a sound-guided task, sound specific neuronal patterns in the auditory cortex may precede the replay of corresponding place cells in the hippocampus [69]. Future work will investigate the origin of this spontaneous activity and the coherence of signals across sensory modalities with the hippocampus around SWRs.

Acknowledgments

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Papers of interest

*Ajabi et al., 2022, *in review*
Recording from large ensembles of HD cells in the ADN, this study shows that the gain of the ADN-HD networks is modulated with respect to the presence of cues and that the gain of the HD attractor network is intimately related to the angular speed of the HD signal during reorientation.

** Chaudhuri et al., 2019
Using advanced mathematical analysis, this study provides evidence for attractor dynamics within the HD cell network.

** Gardner et al. 2019
Recording from ensembles of grid cells across brain states, this study demonstrates that grid cells maintain their mutual coordination during sleep. Like HD cells, this coordination is compressed in time relative to wakefulness and REM sleep. See also Trettel et al., 2019.

* Gent et al., 2018.
This study shows that the ADN is a key node for the synchronization of UP states in the medial and posterior cortex.

* Levenstein et al. 2019
Using a combination of data analysis and computational modeling, this study shows how the hippocampus and the neocortex interact during NREM sleep, specifically how SWRs are coordinated with the UP-DOWN state dynamics in the neocortex.

* Ólafsdóttir, 2016
Recording simultaneously from CA1 and deep layers of the MEC, this study shows that replay of spatial trajectories is coherent between the two structures. See also O"Neil et al., 2017

* O'Neil et al., 2017
Recording simultaneously from CA1 and superficial layers of the MEC, this study shows that replay is not coherent between the two structures. See also Ólafsdóttir et al., 2016

** Trettel et al., 2019
Recording from ensembles of grid cells across brain states, this study demonstrates that grid cells maintain their mutual coordination during sleep. Like HD cells, this coordination is compressed in time relative to wakefulness and REM sleep. See also Gardner et al., 2019.

** Peyrache et al. 2015
This study demonstrates that ensemble of HD cells in the ADN-PoSub network maintain their coordination across brain states, with HD cell showing 5-10 faster dynamics during NREM than during wake/REM.

* Vantome et al., 2020.
Using a combination of slice recording, optogenetics, and in vivo manipulation, this study shows that the PoSub exerts a strong feedforward inhibitory effect on the ADN.

** Viejo and Peyrache, 2020.
By recording from ADN-HD cell ensembles of hippocampal LFP simultaneously, this study show that ADN-HD cell population increases in gain and stabilizes its internal representation immediately before SWRs.

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