Hippocampus and Parietal Cortex Activity Patterns Encode Coordination Between Map-Like and Body Centered Navigation

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Introduction:

Navigation is a central part of living in today's society. Simply deciding to turn left or right at an intersection to go home or to your favorite restaurant involves many complex mechanisms in the brain. These decisions are made from both egocentric (first-person) and allocentric (third-person) [1], [2], [3]. A disruption in spatial awareness is one of the first symptoms to show in Alzheimer's disease, and thus it is our goal to learn more about how these brain systems work in normal animals so we can understand disease related perturbations.

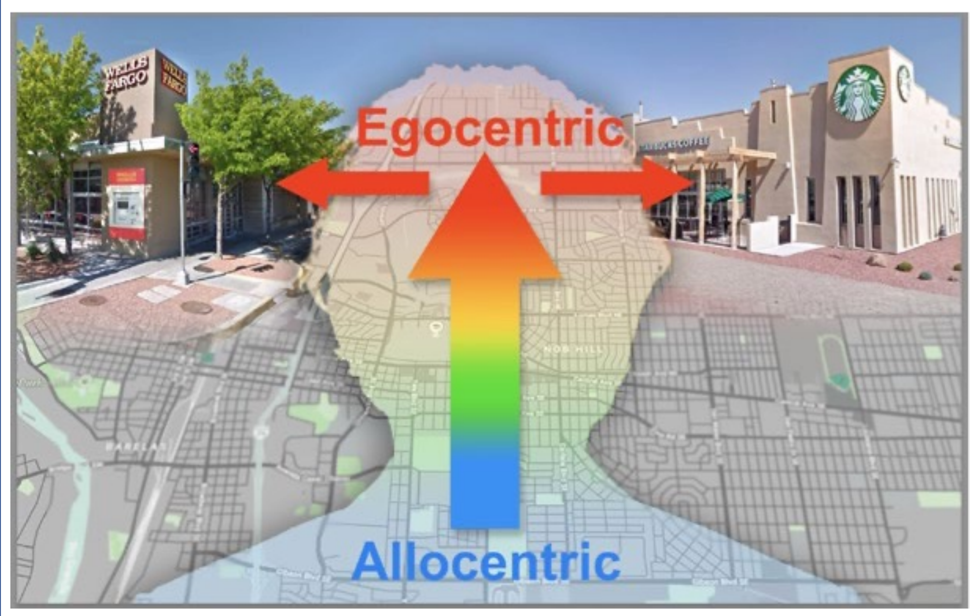

Fig 1. Coordination between allocentric (map-like) and body-centered (egocentric) frames of reference. Our brain performs navigational computations that can operate sequentially or in parallel mapping our position in allocentric coordinates. However, our interactions with the world are body-centered or egocentric by nature (e.g., we turn right at a particular intersection). A fundamental problem is how these frames of reference interact. For example, the action taken at a common city intersection (turn left vs. turn right) is dependent on knowledge of a distant goal location and one's allocentric location in an environment (approaching the intersection from the north).

Methods:

- **Alternation Task Training**
  - Our rat, RFB025, was trained to run back and forth on a track for a food reward
- **Random Lights Training**
  - Circular arena set up with evenly spaced lights and reward stations around circumference and distal cues distributed around the walls of the room
  - RLB025 was trained to run a randomly activated light for a food reward
- **Complex Spatial Sequence Task (with food motivation)**
  - Next, incorporated a repeating pattern of the order the lights flashed. For memory/test trials the cue lights only come on after a 7s delay, so to obtain rewards quickly the rat must run through the sequence uncued. Well trained rats can do this with >90% accuracy
  - Sequence followed 1-2-3-4, 1-2-3-5) pattern with choice points at 4 and 5
  - We trained RLB025 to memorize the pattern and run reliably to the correct zones without immediate light cues
- **Surgical implant of stimulating and Recording Electrodes**
  - We implanted electrodes into the reward center of the brain to replace food motivation
  - The implant also included 21 4-wire recording electrodes distributed across parietal cortex and hippocampus
- **Stimulation-box Training**
  - After surgery recovery, we manipulated the stimulation's frequency and current to find an optimal stimulation that motivated RLB025
- **Complex Spatial Sequence Task (with stimulus motivation)**
  - We repeated the task but replaced food motivation with reward stimulation through the implant

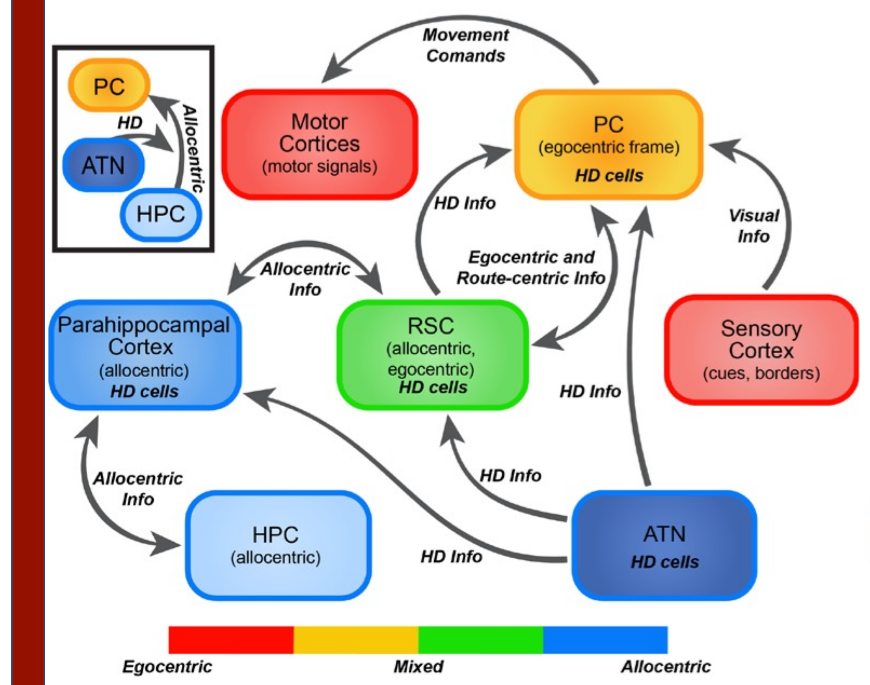

Fig 2. PC, HPC, and ATN Are anatomically and functionally well-positioned to interface between egocentric and allocentric frames of reference within a larger network. Illustration of the general pattern of an anatomical connectivity and the functional shift frames of reference encoded by the brain regions that comprise the extended HPC-ATN-PC network. HPC and para-hippocampal regions (entorhinal cortex, postsubiculum, and parasubiculum) encode an animal's position in space predominantly in allocentric or map-like coordinates. The PC interfaces between egocentric actions, and allocentric spatial and HD information. The ATN provides allocentric HD information..

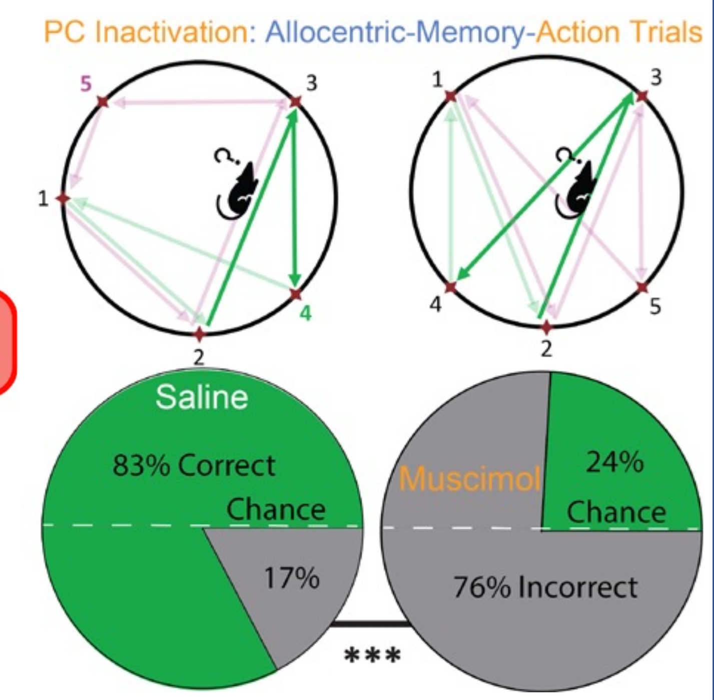

Fig 3. PC is critical for transforming allocentric context into egocentric actions. Percent correct for PC saline and muscimol sessions for two variations of the *complex spatial sequence task*. When learning to generate the egocentric action for the allocentric context, rats tend to form a bias towards one of the actions. In this case the rat developed a bias for the zone 3-5 segment such that no errors were made for that element (not shows). However, muscimol infusion significantly impaired 3-4 element performance versus saline. ***P<0.00001 n=2 rats.

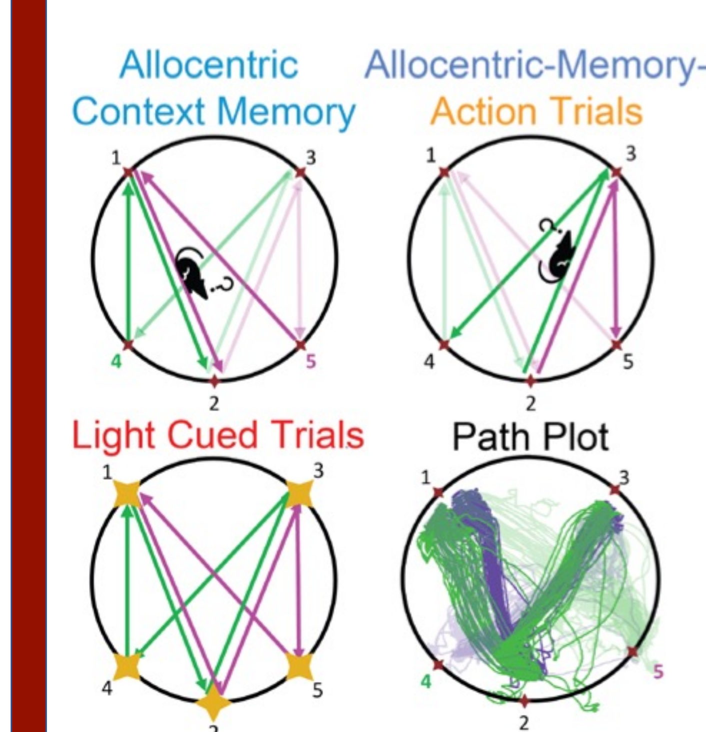

Fig. 4. Complex Spatial Sequence Task. Schematic for the repeated elements sequence in the *complex spatial sequence task*. Zones are numbered clockwise starting at the top left. The rat always starts at zone 5 and continues to zone 1-2-3-4-1-2-3-5. There are at least 4 critical components of this task. *Top Left.* When traversing through zones 1-3 the rat must keep track of its allocentric spatial context to coordinate the memory for allocentric context with the correct egocentric action to reach zone 4 or zone 5 (*Top Middle). Top Right.* Test trials where the rat navigates through the sequence using allocentric orientation are interleaved with light cued trials (both in sets of two) in which the rat is led through the sequence by sequentially active light cues. *Bottom left.* Allocentric memory only trials in which the rat only needs to remember the location of zone 1. *Bottom Right.* Same path plot but only for the 1-2-3 segment and color coded for cued vs Non-Cued trials. Paths on the 2-3 segment again completely overlap for light cued vs. memory trials. Representative example from n=2 rats and 7 data sets when performance was close to 70% correct.

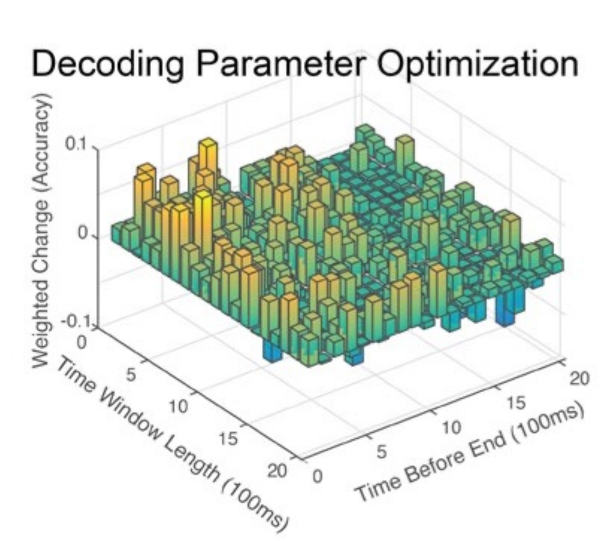

Figure 5. Decoding parameter selection. A parameter search is performed by combining decoding runs from both brain regions and adjusting the window size and time before zone 3. The peak value is selected, and those parameters are applied to decoding runs for each brain region (unless there are multiple distinct peaks in the parameter space). Data from another unpublished study. n=5 control mice.

Results:

Training Bias:

- During training, we found that 025 had developed a bias towards one of the choice zones (zone 4 vs. zone 5 in the pattern). This was expected because all previous rats have developed a similar bias (through which zone is biased 4 vs 5 varies across rats).
- Following an adoption of intermittent rewarding where he was not rewarded for navigating to incorrect zones, we saw a decrease in that bias more towards an even distribution of correctly navigating towards each zone 4 vs. zone 5.

Stimulus Results:

- Following surgery, RLB025 was put through a stage of training where we attempted to determine the most effective stimulus through the electrodes that have been placed into the reward center of the brain.
- We found that a stimulus to the brain's reward center at a 141 hertz frequency and a current of 30 amperes had the best result without artifacts, or unwanted motor cortex stimulation.
- Unfortunately, none of the stimulation parameters were as motivating as food reward, so we returned to food rewards.

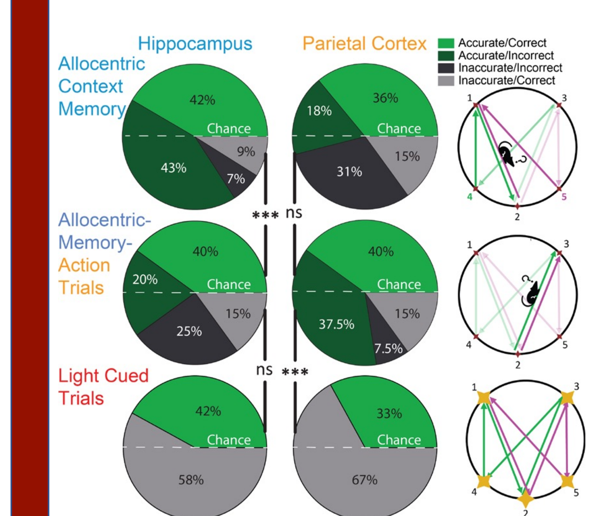

Fig. 6. Activity patterns in the HPC signal allocentric context memory while PC signals correct performance and error trials for allocentric-memory-action trials. *Top.* A leave one out decoding approach was used to build a model from HPC (*left*) or PC (*right*) cell activity during the zone 2-3 traversal to predict spatial allocentric context memory (cam from zone 4 or 5). HPC cell activity is highly accurate at decoding spatial context (i.e., correctly predicting which zone the rat came from zone 4 or 5); however, PC decoding was significantly less accurate. *Middle.* The same approach was used to build a model from PC MUA (*Right)* to predict the future choice for the zones in the sequence which require translating the spatial context memory into the appropriate action (zone 3-4 and 3-5). PC MUA was highly and equally accurate in predicting both correct (light green) and error (dark green) trials (78%) versus inaccurate decoding of correct (light gray) and incorrect (dark gray) trials. HPC decoding performance for zone 3-4 and 3-5 was lower than PC and worse than for the allocentric context memory. *Bottom.* When the same analysis was performed for the interleaved sets of trials where a cue light led the rat through the sequence, decoding accuracy remained low for HPC Left) and was significantly lower for PC (Right), suggesting HPC and PC are less critical for cued navigation. n=2 ** p<0.01. ***p<0.001.

Conclusion:

From the current findings from these experiments, we have made significant progress in setting up the foundation for further testing to be conducted. We successfully trained our rodent model to navigate through various tasks which test the abilities of the hippocampus and the parietal cortex. Surgical implants have allowed us to more finely manipulate the reward in the model as well as track the brain activity during pre-sleep, task, and post-sleep stages. In the future, we will continue to fine-tune our electrode stimulus to verify past findings in mouse models and translate them to our current model organism with hopes of bringing conclusions to human neuroscience. Our goal is to add to our current data set with this animal so that we may draw statistically valid conclusions from the data we have collected thus far. We predict that preliminary data will hold true, and these brain regions will be critical for both remembering the allocentric context (hippocampus) and converting this information into the appropriate egocentric action (parietal cortex).

Acknowledgements:

Thank you to Dr. Aaron Wilber for mentoring me through his research project and to graduate students Christine Simmons and Yicheng Zheng for your support and training.

References:

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