Age-related changes in medial prefrontal cortex-ventral hippocampus theta power interactions during a spatial working memory task

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Introduction

Neuronal ensembles in the hippocampus (HC) and medial prefrontal cortex (mPFC) play a critically important role in memory-based navigation and decision making, a process susceptible to decline with age in mammals. These regions are connected via a unidirectional monosynaptic projection from the ventral CA1 region of the hippocampus to the mPFC, and damage or inhibition of this circuit leads to impairments in spatial alternation tasks (Wang et al., 2006). Rats with mPFC lesions show impaired performance on spatial working memory tasks (Kim et al., 2009), while rats with hippocampal lesions are impaired in both spatial memory and working memory tasks (Sapiurka et al., 2016). To test how interactions between these regions are affected with increasing age, we used a spatial alternation task consisting of two interleaved components: an "inbound" component evaluating spatial memory, and an "outbound" component evaluating working memory. The inbound component is primarily dependent on the hippocampus. The outbound component utilizes the prefrontal cortex in order to maintain a working memory of the previously visited arm as well as the hippocampus to locate the current goal position in space. Behavioral data from young (10-13 mo) and old (24-26 mo) rats tested on this task indicated that aged rats are slower to learn both the inbound and outbound components of this task. Furthermore, a significant deficit was observed in the aged rats' performance on the outbound component even after reaching the learning criteria for the task. As the outbound component of this task requires coordination between the hippocampus and mPFC, interactions between these regions could be impaired in aged rats. We investigated the mechanisms underlying age-based performance on this task by implanting young and old rats with hyperdrives in both structures. Electrophysiological recordings were collected from the ventral CA1 region of the hippocampus (vHC) as well as both the prelimbic (PL) and infralimbic (IL) regions of the mPFC as rats performed the spatial alternation task. Looking at electrophysiological activity prior to task choice points, we observed strong theta (8-12Hz) activity in both the vHC and mPFC regions in young and old rats. Through these simultaneous electrophysiological recordings of these two regions, we investigated differences in mPFC and vHC theta power both within regions as well as theta power coherence between regions across age groups in order to identify potential differences in neuronal synchronization.

Recording Locations and LFP Activity

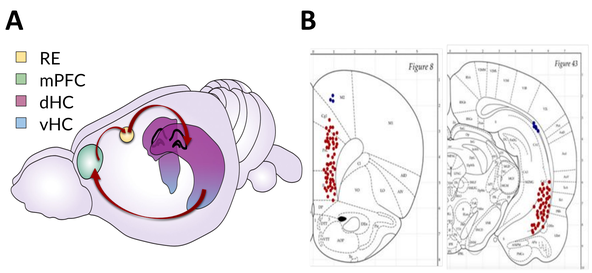

Fig 3: A) A schematic representing the rodent brain with the dorsal to ventral hippocampus represented in purple and blue respectively. The ventral hippocampus directly projects to the mPFC represented in green which projects back to the dorsal and ventral regions via the thalamus. **B)** The Paxinos images represent the mPFC on the left and ventral HC on the right (Paxinos and Watson, 1998). The red dots represent the recording locations of the tetrodes for a rat across sessions and the blue represents the location of the local reference tetrode.

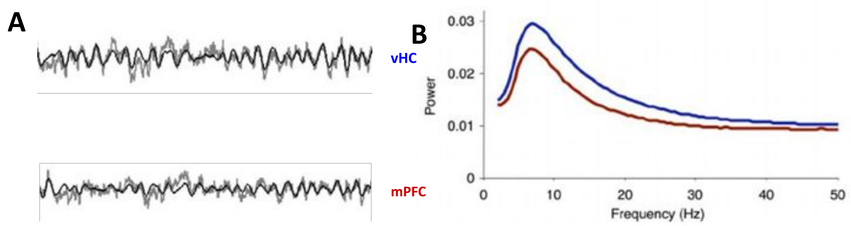

Fig 4: A) A representational trace of the local field potential activity from the ventral hippocampus and mPFC are in grey. The black line represents a bandpass filtered trace of 0.1-60 Hz to better visualize the theta oscillation at 8-12Hz. **B)** A representation of a power spectrogram on the local field potentials depicting a peak at 8-10Hz in the mPFC and vHC.

Theta Power

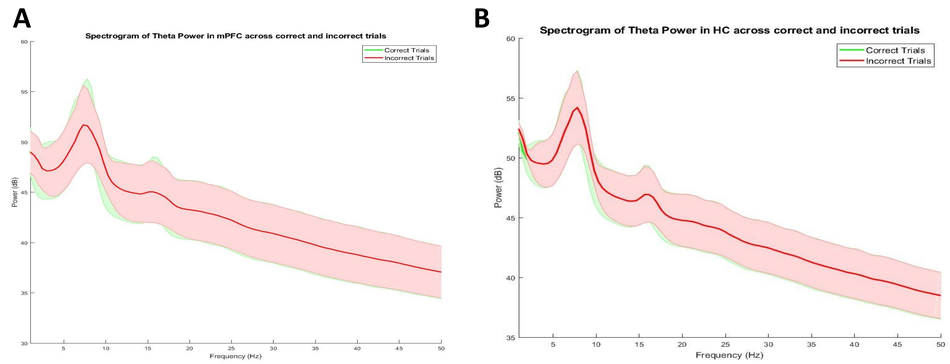

Fig 6: Theta power recorded from **A)** mPFC and **B)** HC in old (n=3) and young (n=7) rats during both correct (green) and incorrect (red) trials. 3 sessions were analyzed per rat. Shaded areas outside of the line represents a 95% confidence interval for theta power.

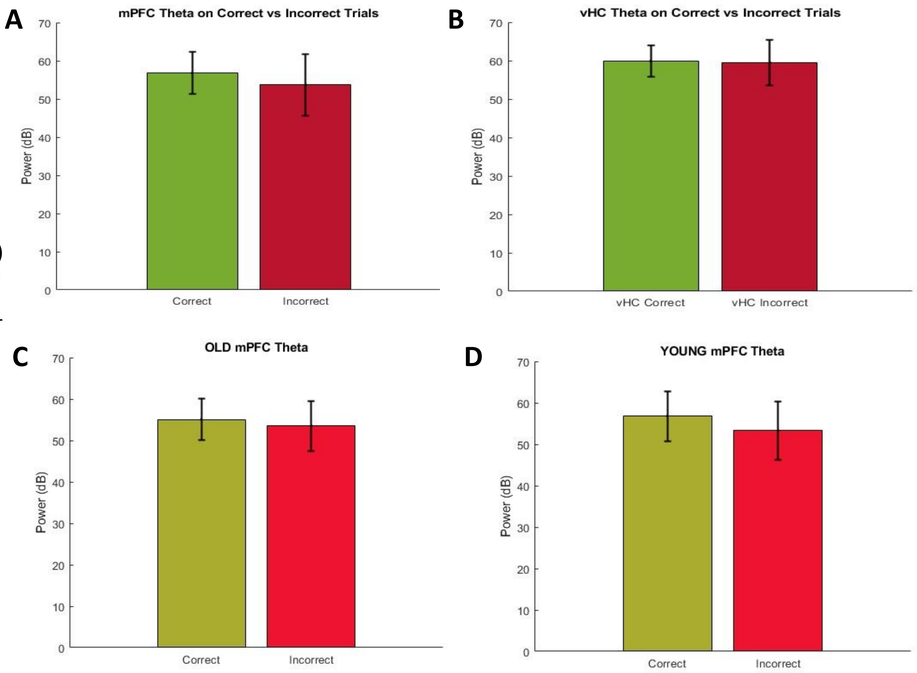

Fig 7: Bar graphs representing differences in peak theta power in **A)** mPFC and **B)** vHC in both young (n=7) and old (n=3) rats, 3 sessions per rat. No significant differences can be seen in theta power for either brain region dependent on trial performance. Peak theta power across age was also analysed in the mPFC for both **C)** old and **D)** young rats for correct and incorrect trials. No significant differences can be seen in theta power in either age group based off of performance.

Behavioral Task

The behavioral apparatus consists of a W-shaped track comprised of three identical arms, with a small food dish at the end of each arm. Infrared sensors along the track monitor the position of the rat, and signal the release of a liquid food reward upon a correct arm visit. A figure of the W-maze spatial alternation task can be seen below as figure 1. Returning to the center arm from an outer arm is labeled as an inbound trial, and moving from the center arm to the less recently visited outer arm is labeled as an outbound trial. The inbound component is primarily reliant on hippocampus-dependent spatial memory. The outbound component uses both the hippocampus for spatial information and the prefrontal cortex to maintain a working memory of the most recently visited arm. If the rat does not visit the correct outer arm, they are not rewarded and must return to the center arm to restart the trial. The session in which an animal has reached learning criteria is the trial when the animal reaches above chance performance (50%), and remains above chance performance for the following two trials. This initial session is hence determined as the "learning session."

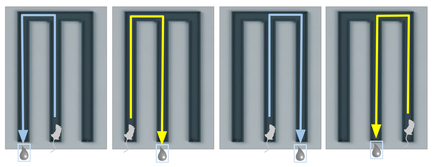

Fig 1: A schematic diagram of a correct progression of the W-Maze spatial alternation task across trial periods. The rat is placed at the bottom of the center arm at the start of a trial. **A)** After running to the end of the center arm and receiving a reward, the rat must visit one of the two outside arms, **B)** then return to the center arm **C)** and visit the opposite outside arm. **D)** The rat will then return to the center arm and repeat.

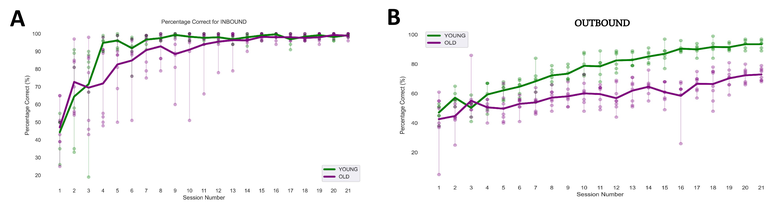

Fig 2: Percentage correct on the **A)** inbound component ($F(1,24) = 1.9$, p-value = 0.33) and the **B)** outbound component ($F(1,24) = 33.42$, p-value < 0.001) of the W-Maze spatial alternation task. While old rats (n=5, purple) and young rats (n=9, green) are both able to reach close to 100% accuracy on the inbound component, old rats learn the inbound component significantly slower than young rats and make significantly more errors than young rats on the outbound component even after reaching the learning criteria for the task.

Rat Trajectory Analysis

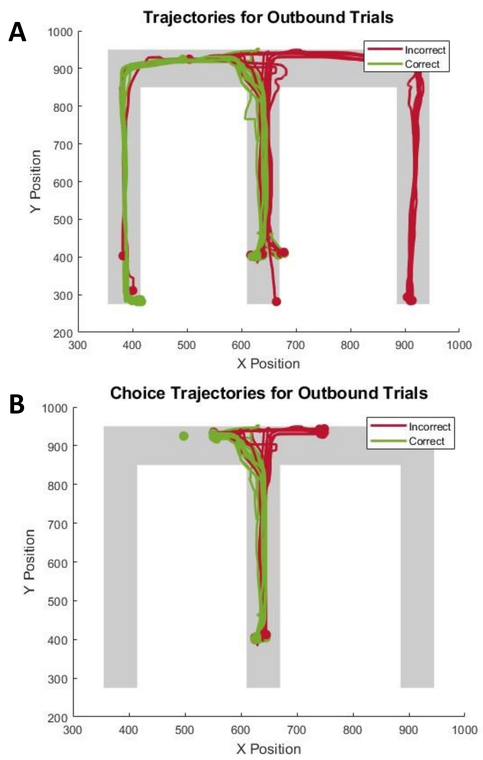

Fig 5: A) Example trace of trajectory of a rat on outbound trials when moving with a velocity of >1m/s. The red represent incorrect trials and the green the correct trials. **B)** Example trace of the trajectory of a rat on outbound trials restricted to the choice point.

Conclusions

- Old rats are significantly slower to learn the inbound component of the W-Maze spatial alternation task, and perform significantly worse on the outbound component of the task after reaching learning criteria.
- Initial analysis of sessions indicates no significant differences between theta power in either the mPFC or vHC based on task performance of rats. When further investigating potential differences in regional theta power by age, no significant differences in peak theta power is observed in the mPFC based on task performance in either age group.
- The conclusions are based on only a fraction of the total number of sessions collected from these rats, and additional animals have not yet been analyzed. Thus, the final conclusion from this experiment may differ from this subsample, although these preliminary results may be confirmed. Furthermore, we plan to investigate potential differences in theta power when restricting the region of analysis to choice point on outbound trials.

References

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Acknowledgements

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