Mice in the Manhattan Maze: Rapid Learning, Flexible Routing and Generalization, With and Without Cortex

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Abstract

Mice are flexible foragers in the wild and quickly adapt to environmental changes. Here we designed a novel navigation task, the "Manhattan Maze," to study cognitive flexibility in mice. The Manhattan Maze is easily reconfigurable and allows systematic task designs through search algorithms in a vast space of 2^{121} possible maps. Within two days, completely naïve wildtype mice learned three complex maps, each taking a sequence of nine turn decisions to solve. On Day 1, they rapidly learned the first map after ~ 10 round trips. On Day 2, they retained the ability to solve the map that was repeated. Further, they accelerated at learning new maps. We then tested the maze on acortical mice, a structural mutant born without the hippocampus and most of the neocortex. Although their initial solution took $\sim 3\times$ longer than wildtype, acortical mice successfully learned multiple maps and approached optimal performance. Surprisingly, they also learned new maps faster and were able to solve the same maze configuration when repeated after two months. Our results suggest that the mice can rapidly learn and that the cortex is not strictly required for navigating the Manhattan Maze.

Keywords: navigation; rapid learning; cognitive flexibility; generalization

Introduction

Rapid learning and cognitive flexibility are crucial to survival in an ever-changing world. As model organisms for neuroscience research, rodents are adept at complex navigation tasks such as mazes (Tolman, 1948). For example, mice make thousands of navigation decisions and learn a 10-bit sequence of choices after fewer than ten reward experiences (Rosenberg, Zhang, Perona, & Meister, 2021). Rats can solve three or more different mazes within a day and develop near-optimal paths in a few trials (Hebb & Williams, 1946; Rabinovitch & Rosvold, 1951; de Cothi et al., 2022). These results suggest that mazes are valuable for studying learning and flexibility that occur at a short temporal scale in changing environments. Compared with the performance in traditional learning tasks that take weeks and months of training, the speed of cognition in mazes is more homologous to the timescale of human capacity and therefore informative for cross-species comparisons.

In humans, regions of the neocortex and hippocampus are considered responsible for different subdomains of cognitive flexibility and control (Logue & Gould, 2014). The interplay between the neocortex and hippocampus is necessary for forming, retaining, and recalling memories. It has not been determined whether the vital role of the cortex also holds for rodents.(Laubach, Amarante, Swanson, & White, 2018).

Here we devised a novel maze framework, the Manhattan Maze, to probe into the learning capacity and cognitive flexibility of rodents. The maze design was inspired by the typical grid-like street plan of urban districts, such as Manhattan Island in New York City. The principle of the maze design is to restrict accessible junctions, achieved by separating the perpendicular corridors into different layers and selectively connecting them via a mask (Fig 1A). In this study, we used an 11×11 two-layered Manhattan Maze, which allowed $2^{11\times11}$ possible corridor combinations – a vast space of possible maps on the order of 10^{36}. We designed a two-day experiment protocol that introduced three complex maps, each requiring a unique sequence of nine turn decisions to solve. We

first tested the maze on C57BL6/J mice that were behaviorally naïve. The mice were water-deprived for 20-22 hours and expected to forage for rewards from two water ports (”Home” and ”Out”) located at the periphery of the maze.

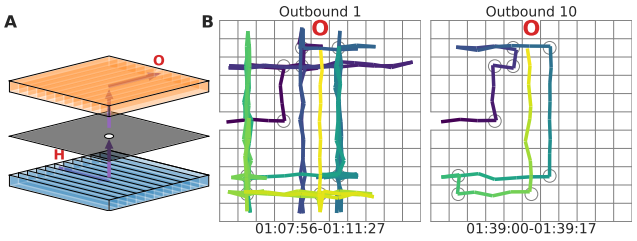

Figure 1: A. The 3D structure of the Manhattan Maze. Corridors in the bottom (blue) layer and the top (orange) layer are perpendicular to each other and connected by a mask (grey) with hole(s). A mouse alternates between ”Home” (H, red) and ”Out” (O, red) to obtain water rewards. B. Two outbound traverses (rewarded run from H to O) in Map A by one mouse. The time information for each plot counts the time spent in the maze from the beginning of the session.

Results

On Day 1, naïve mice learned the first nine-decision map within a few rewards. After 10 round trips and half an hour, the example mouse in Fig 1B shortened its traverses (i.e. rewarded runs between two water ports) to $\sim 10\%$ of its first attempt. The learning process unfolded over three distinct phases (Fig 2A,). Phase 1 (P1) marked zero-shot learning: the first homebound journey (#2) was drastically ($\sim 50\%$) shorter than the first outbound (#1), even though the mice had never traveled in this direction before. In Phase 2 (P2), the improvement became gradual when the mice improved at making correct turns (Fig 2C). At this stage, the homebound traverses were still shorter and of fewer errors than the preceding outbound ones. Traverses in both directions stabilized in Phase 3 (P3), with occasional long exploratory runs from individual mice.

On Day 2, the animals retained the ability to solve the previously seen map and learned new maps faster. For those repeating the old map, their first traverse took a similar amount of time to the stable performance on Day 1 (Fig 2B blue vs. Fig 2A grey). New maps (Fig 2B red and green) were learned within ~ 3 round trips (7 traverses, dashed line), after which their performance was indistinguishable from the old map. This reflected a faster learning rate in new environments, a phenomenon often termed ”generalization” or ”meta-learning”. The effect of memory and generalization was also visible when measured by the error rate of turns (Fig 2D-F). Compared to the same time points on Day 1 (Fig 2D), on average one fewer turn mistakes were made in both new and old maps (Fig 2E), and the memory of the old map gave a visible advantage (blue vs. red and green). In late sessions on Day 2

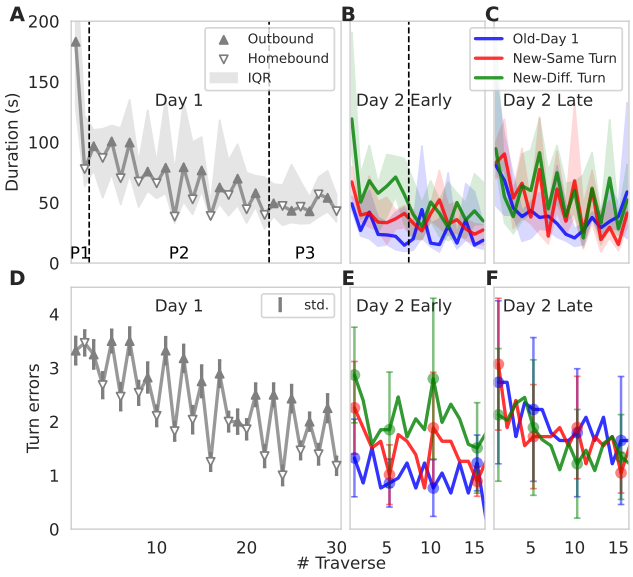

Figure 2: Two-day task performance of the wildtype mice. A-C. The duration of traverses shortened over traverses (median and IQR, n=28) B. Early on Day 2, the traverses in the old map (blue) were shorter than Day 1 (A) and the new maps (red and green), but only for the first 7 traverses (left to the dashed line). C. Late on Day 2, the differences between the old and new maps were no longer significant. D-F. Fewer turn errors (mean and std.) were made over traverses. E-F. The learning curves between the new maps with the same (red) and different (green) turn sequences were not significantly different.

(Fig 2C and F), the differences between maps dissipated after multiple maps were seen, although the error rate and duration of runs increased slightly. These results indicate that the mice favored a flexible learning strategy that benefits learning all maps over rote memories of individual maps.

To investigate whether learning turn sequences would benefit meta-learning, we designed the turn sequences of the two new maps to be either the same (red) or different (green) from the old map (blue). The differences in learning between the two maps were marginal in early sessions (Fig 2B and E) and indistinguishable in late sessions (Fig 2D and F). We conclude that the mice did not generalize by memorizing turn sequences.

Surprisingly, the observed behaviors in the Manhattan Maze did not require the neocortex or hippocampus. We tested the maze on an acortical mouse mutant born without a hippocampus and most of the neocortex (Kim et al., 2010) (Fig 3A). Compared to the wildtype mice (Fig 2A), the acortical mice took 2-3 times longer to solve the maze (Fig 3C). However, they eventually succeeded in learning the optimal paths in multiple maps (Fig 3B) and also accelerated at learning new maps (Fig 3C). In addition, one mouse retained a robust ability to obtain rewards in the same map over two months (Fig 3D), able to solve it immediately upon re-exposures, even af-

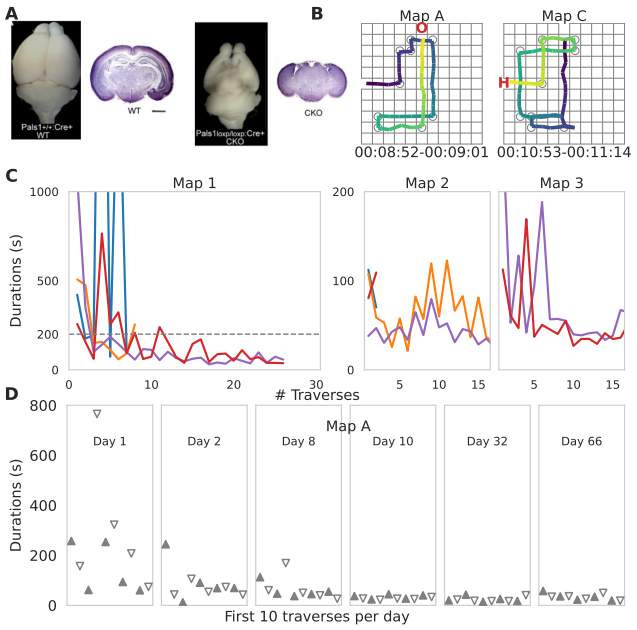

Figure 3: A. Histology of a wildtype vs. acortical brain (Kim et al., 2010). B. The shortest traverses developed by an acortical mouse in two different maps. C. The learning curves in the 1st, 2nd, and 3rd maps seen by the acortical mice became steeper (one line per mouse, colors correspond to individual animals). D. An acortical mouse retained the ability to solve Map A over months.

ter a 34-day break. These findings suggest that the remaining brain structures in the mutant mice were sufficient to support learning and navigation in the Manhattan Maze.

Conclusions and Future Directions

Our study presents a powerful tool for studying cognition in rodents. We observed that the mice developed faster solutions to complex and changing environments over just two days of their lives. We also point out that the contribution of the neocortex circuit architecture to cognitive flexibility is not indispensable for mice. This highlights the need to unravel the underlying circuit mechanisms that support these cognitive processes. Our data also set a benchmark for navigation models and machine learning algorithms, especially for those interested in transfer learning, few-shot learning, and meta-learning.

Acknowledgments

This project is funded by Simons Collaboration on the Global Brain (SCGB 543015 and 543025).

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