Generalisation of structural knowledge in hippocampal – prefrontal circuits

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Summary
A hallmark of intelligence is the ability to generalise previously learned knowledge to solve novel analogous problems. For instance, someone who knows how to drive a car in Europe can quickly adapt to driving in the U.K without having to relearn driving from scratch simply because some rules and motor actions are different. Such transfer of knowledge relies on formation of representations that are abstracted from sensory states and humans excel at this task. However, little is known about whether other animals can learn abstract representations that are detached from sensory experience. Even less is known about how the brain represents such abstract representations while maintaining the content of individual experiences.

Here we present a novel behavioural paradigm for investigating generalisation of structural knowledge in mice, and report preliminary electrophysiological findings from single neurons in hippocampus and prefrontal cortex. Mice serially performed a set of reversal learning tasks, which shared the same structure (e.g., one choice port is good at a time), but had different physical configurations and hence different sensory and motor representations. Subjects’ performance on novel configurations improved with the number of configurations they had already learned, demonstrating generalisation of knowledge. As in spatial remapping experiments, many hippocampal neurons responded differently in different configurations – here tasks rather than spatial environments. In contrast, preliminary analyses suggest prefrontal representations were more general and reflected different stages of the trial irrespective of the current physical configuration.

Additional detail
Mice were trained to solve a probabilistic reversal-learning paradigm where they initiated a trial by poking in one port, then chose between two other ports for a probabilistic reward (Fig 1a). Once the subjects consistently chose the high reward probability port, the reward contingencies reversed. When subjects had competed ten reversals on a given port configuration (termed a ‘task’), they were moved on to another task with a different port configuration (Fig 1b). All of the tasks shared the same trial structure (initiate \( \rightarrow \) choose) and a common abstract rule (one port has high and one low reward probability, with occasional reversals) but the specific location of the ports and hence the actions required to perform trials were different in each configuration. Mice got better at tracking the good poke over the course of each physical configuration of the task (i.e. fewer trials to criterion), but critically also showed improvement across tasks with different configurations (Fig 1c). Moreover, subjects also got better at following within trial structure (initiate \( \rightarrow \) choose) across tasks, making less pokes to invalid ports (Fig 1d). This demonstrates generalisation of learning, and suggests that mice may have developed sensory invariant/abstract representation of the structure of the task. We used silicon probes to record from hippocampal CA1 (679 neurons, \( n = 4 \) mice) and prefrontal cortex (848 neurons, \( n = 4 \) mice). In recording sessions mice typically performed at least 4 reversals in each of 3 different configurations (Fig 1e).

![Figure 1: Generalisation of structural knowledge in mice. a) Trial structure of the probabilistic reversal-learning paradigm. Mice poked in an initiation port then chose between two choice ports for a probabilistic](image-url)
reward. Reward contingencies reversed after the animal consistently chose the ‘good’ port. **b)** Example configurations used in each task. Subjects completed 10 reversals on each layout before moving to a new poke port layout. **c)** Median number of trials mice took to reach the reversal threshold on each task configuration of a reversal-learning problem. Mice reached criterion in fewer trials across task configurations. **d)** Median number of pokes per trial mice made to a choice port that was no longer available because they already chose the other choice port. Mice got better at following within trial structure across configurations. **e)** Example of the configurations used in a single recording session. Mice typically completed three configurations each consisting of four reversals in each recording session.

Our preliminary analyses show that a substantial proportion of hippocampal neurons fired selectively when mice entered a particular physical port (Fig 2a, cell 1). However, when the task configuration changed, the activity of many hippocampal units remapped. Some units fired at a given port in one configuration but not when the same port was visited in a different configuration (Fig 2a, cell 2). Other units fired selectively to one of the choice ports in each configuration (Fig 2a, cell 3). In contrast, prefrontal representations appeared to be more invariant across configurations. Many cells fired selectively when one of the choice ports was rewarded irrespective of its location in all three tasks (Fig 2b, cell 1). We also found units that fired at the shared port in all tasks irrespective of whether it was rewarded or not (Fig 2b, cell 2) and neurons that had multiple peaks throughout the trial (e.g., selective for both initiation and choice states) irrespective of the task layout (Fig 2b, cell 1). PFC cells therefore appeared to represent task states irrespective of the physical locations of the ports. We are working to develop formal ways of quantifying how task general and configuration specific information is represented in the neuronal populations.

**Figure 2:** Example neurons from CA1 and PFC. Upper panels show normalized mean firing rates aligned to choice time. Colours indicate configuration (green, blue, pink). Vertical dashed lines indicate initiation (grey), choice (black) and outcome (pink) times. PFC cell 1 and 2 were split by rewarded and non-rewarded trials. Solid lines indicate mean firing rates on rewarded trials, dashed are rates on non-rewarded trials. Lower panels show heat maps of normalised firing rate as a function of time within trial and trial number. Configurations are indicated on the right. **a)** ‘Place cell’ like firing and ‘remapping’ in hippocampus. Cell 1 is a spatial cell firing at a particular poke across all three configurations. Cell 2 is a ‘remapping’ cell that only fires at the far right port in the context of one of the configurations. Cell 3 fires at different choice ports in different configurations. **b)** Sensory invariant representations of trial structure in prefrontal cortex. Cell 1 is active at one of the choice ports when it is rewarded in all configurations. Cell 2 fires at the shared choice port in all configurations. Cell 3 is active at both initiation and choice ports across all configurations.