The Hex-Maze: A previous knowledge task for mice

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Abstract

New information is rarely learned in isolation, instead most of what we experience can be incorporated into previous knowledge networks. However, most rodent laboratory tasks assume the animal to be naïve with no previous experience influencing the results, which may be a factor contributing to the current crisis of translational failure when going from the basic lab to human research. Previous research in rats has indicated, that previous knowledge in form of a schema can facilitate knowledge acquisition and accelerate systems consolidation: memories become more rapidly hippocampal independent and instead rely on the prefrontal cortex. These results emphasized the need for more tasks that investigate previous knowledge effects and can be applied in both rats and mice. Here, we developed a new spatial navigation task, training food locations in a large, gang-way maze – the Hex Maze. Analysing both with and across session performance, we can show simple memory effects as well as multiple effects of previous knowledge accelerating both online learning as well as performance increases during offline periods. These effects are reminiscent of both Learning-Set and Schema, two different previous knowledge effects described previously in the literature.

Introduction

After infancy we rarely learn new information in isolation, instead most of what we learn throughout our lives can be associated with previous knowledge. This is also one of the largest discrepancies between human and rodent research: while most human tasks are embedded in familiar things, rodents tend to be naïve to the behavioural tasks and can draw only little benefit from previous experience.

This distinction is critical since the rate of learning and consolidation as well as neural underpinnings and relevant brain areas can show a shift in the presence of previous knowledge (Squire et al. 2015; Genzel et al. 2017). In human research the previous knowledge effect has been long established, but it was not introduced to neuroscience until the seminal study of paired-associates tasks introducing the schema effect on systems consolidation (Tse et al. 2007). In a sequence of papers it was shown that previous knowledge accelerates learning to a 1-trial event as well as the rate of systems consolidation (hippocampal independency) from weeks to 24-48h (Tse, Langston et al. 2007; Bethus et al. 2010). Further, both the hippocampus and the prefrontal cortex need to be active during encoding for memories to last (Tse et al. 2011; Wang et al. 2012). The involvement of the medial prefrontal cortex in the schema effect was then later confirmed in humans (van Kesteren et al. 2010; van Kesteren et al. 2010; Ghosh et al. 2014; van Buuren et al. 2014). In the original rat study, the authors took special care to ensure that the observed acceleration of learning and consolidation was not due to learning-set effects (Harlow 1949) by comparing the usual training with an inconsistent version of training where flavour-location associations were switched every two days (Tse, Langston et al. 2007). However, despite the very elegant design one criticism did remain: the update event only contained two items (paired-associates) while the original schema training consisted of six such items, making the updates less “difficult” with decreased cognitive load, which could have confounded the effects. Further, the paradigm has also only been established in rats, reducing its applicability to transgenic mouse models in future research.

Later on Richards et al (Richards et al. 2014) used the watermaze to investigate previous knowledge effects, additionally trying to test if systems consolidation leads to a more gist-like quality in memory instead of individual item representation (Hardt et al. 2017), which could not be distinguished in the previous schema task. They trained mice on daily switching platform locations, which were drawn from a pre-determined statistical map in space and could show that search patterns in the watermaze faithfully represented the statistical distribution of platform locations, even more so at 30d than 1d after training. Further, they could show that the prefrontal cortex was necessary for updating behavioural search patterns to conflicting new information in the 30d but not 1d condition (a platform incongruent with the previous pattern). However, no comparison was made to animals without previous knowledge. The Object Space Task (Genzel et al. 2017) uses a similar approach with statistical spatial patterns presented in object configurations instead of platform distribution. The key condition has always an object in one location, with a second object present in one out of three other locations. The final sample and test trial always have the exact same configuration. However at test the animals show a preference for the less often shown location (across the previous sample trials). This shows that both rats and mice are guided by their cumulative experiences across multiple sample trials in their object exploration in a test trial and not by the last sample trial. This once again emphasizes that previous knowledge will affect how an experience e.g. an interference or additional sample trial will affect subsequent performance.

In the present study we aimed at developing a new behavioural task in which we can investigate the role of previous knowledge on new memory acquisition and consolidation across different time-points in training. In order to achieve this it is important that during both initial build-up of the knowledge network (schema) as well as later updates the difficulty and cognitive load remains the same. Thus we chose training mice in a large environment to a single goal location. Different types of previous knowledge effects on performance should be seen: learning the general task

principles (food remains in the same place and I need to navigate there from different positions), enhancing memory encoding (expressed in increased short-term memory and performance on trials 2-end of a session) and enhancing memory consolidation (expressed in increased long-term memory and performance on trial 1 of each session). To test for these different effects we changed goal locations every few sessions. In this task the spatial map of the environment (hexagonal layout, intra- and extra-maze cues) is thought to be the schema that can be – once established – flexibility updated for reward locations or changes within the environment e.g. the blockage of routes with barriers (Arbib 1997).

We could show that mice need 37 sessions (12 weeks) to initially build up this spatial map of the environment that can function as a schema and facilitate rapid long-term consolidation during later updates. Further, in addition to the enhancement of long-term memory and one session learning effect after schema acquisition, we can distinguish a simple memory effect with better performance across the first seven sessions of the first goal location as well as an initial learning-set effect after two weeks of training in the first goal location switch. This initial learning-set effect is not expressed in the first-trial but does facilitate overall session performance to increase. Finally, focussing on our update session we could show that the degree of overlap with previous knowledge influence short-term or working memory performance on the first session of each update, so how quickly new information could be incorporated online during encoding. Thus the Hex-Maze allows to distinguish four effects of previous knowledge on memory, ranging from learning-set to rapid consolidation and within-session updating.

Methods

Subjects

Three cohorts of 4 male C57BL/6J mice each (Charles River Laboratories) aged 2 months, were group housed in the Translational Neuroscience Unit of the Centraal Dierenlaboratorium (CDL) at Radboud University Nijmegen, Netherlands. They were kept on a 12 h light/dark cycle and were pre-training overnight food deprived during the behavioural testing period with a goal of 90% and minimum of 85% free-feeding weight. All animal protocols were approved by the Centrale Commissie Dierproeven (CCD). The first cohort was used to establish general maze and task parameters and entered in the current analysis only in the update phase. All previous training (37 sessions) were to one goal location. Cohort 2 underwent all training, cohort 3 only the build-up and reinforcement phase. All resulting in n=8 for each analysis (Build-Up and Reinforcement coh 2 and 3, Updates coh 1 and 2).

Behavioural Training

After arrival mice were handled daily for 1 week and then habituated to the maze in two 2h sessions (all 4 cage mates together) with intermittent handling for maze pick-ups (tubing). Mice were trained on Mondays, Wednesdays and Fridays. Per training day each mouse underwent 30 min of training in the maze (resulting in up to 30 trials). The maze was cleaned with 70% ethanol and a heap of food (to encourage returning in the next trial, crumbled Kellogg's Coco Pops™) was placed at a previously determined goal location. Start locations for each day were generated based on their relation to the goal location and previous start locations (no repeating locations in subsequent trials, mostly only one shortest path possible, first trial different than previous session last trial, at least 2 nodes distance). On average 30 start locations were needed per day per mouse. All pick-ups in the maze were done by tubing. During probe sessions (always session 2, additionally in Build-Up R1: S7, R2: S5, R3-5 S4) there was no food in the maze for the first and ninth trial and each time for the first 60s of the trial to ensure the smell of the food did not guide them to the goal location. Training consisted of three blocks: Build-Up, Reinforcement and Update (see Fig.1).

Normalized path length was the main performance measure and calculated by dividing the actual path a mouse took by the shortest path between the given start location and the goal location (Fig. 1b). If the mouse was motivated to find the food and developed a knowledge-network of the maze it should navigate the maze efficiently. A score of 1 indicated that the mouse chose the shortest path and did a direct run. Lack of motivation could lead to exploration of the maze rather than running towards the goal location, these trials were identified by noting if the animals did not eat the food at first encounter and were excluded from the analysis. First trial normalized path length was used to measure long-term memory since training sessions were 48-72 hrs apart.

Estimating chance level

For each conducted trial of each mouse, chance level path length was simulated. For each trial parameters was the same for the simulation as for the real mouse of that particular trial. The simulation after start always moved forward and it accumulated a within-trial memory of node-to-node transitions to avoid repeating an already experienced node-to-node transition with the attempt to simulated foraging and novelty seeking behaviour. Thus, at any given choice point, if none of the forward-moving node-to-node transitions had been encountered within the trial the mouse chose its next node randomly among the available forward-moving options. If one of the available forward-moving node-to-node transition had already been encountered within the trial, the simulated mouse chose the other alternative forward-moving option. If all available forward-moving options had previously been encountered within the current trial, then the choice was made towards the least recently encountered node-to-node transition. The memory was reset at the beginning of next trial. For each simulation trial ended once the mouse reached the reward node, and the distance travelled and $path_{norm}$ variables were calculated and this repeated 10,000 times.

Data Analysis

Normalized path length for all trials was calculated using MATLAB 2017b (MathWorks). Repeated measures ANOVAs were run in IBM SPSS Statistics 25 to determine the effect of repeat and session on normalized path length during the build-up and across the three different types of updates. An additional ANOVA was run to investigate changes in within session (trial blocks) as well as first trial performance.

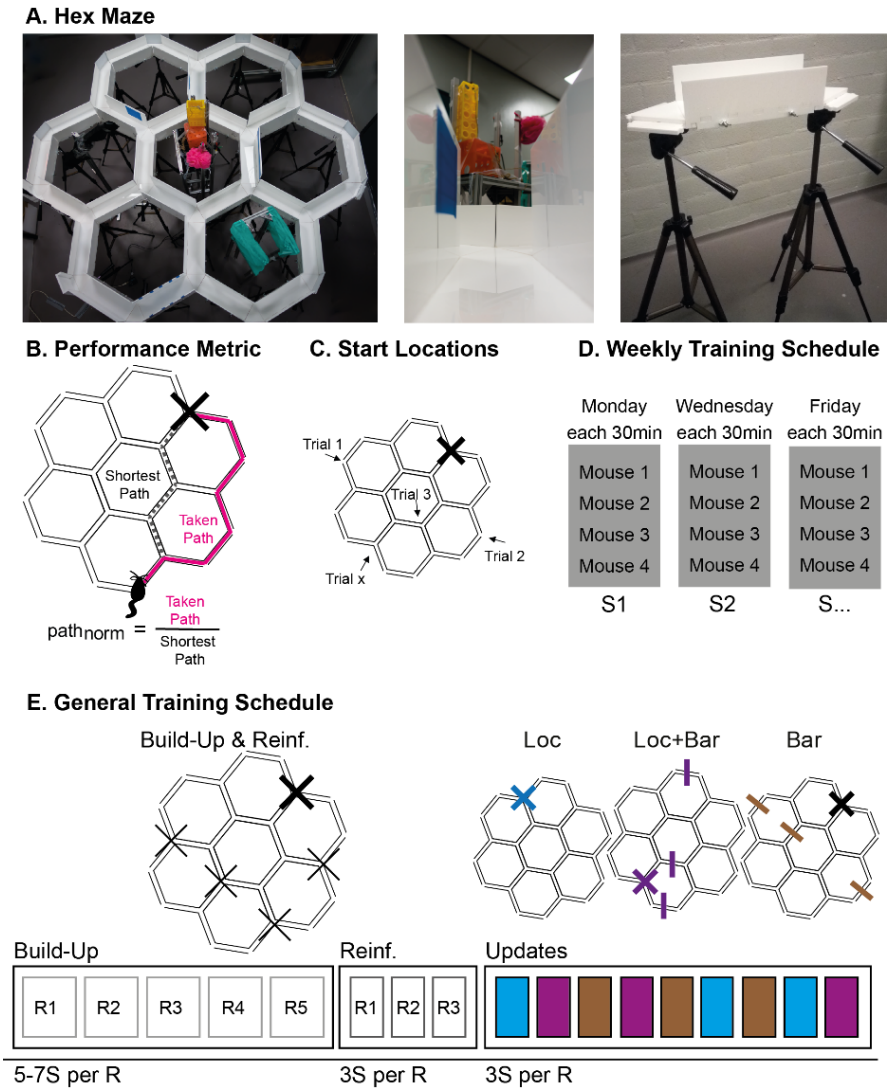

Fig. 1 The Hex Maze: A. shows the maze with intra- and extra maze cues (left), the maze from the view of the mouse (middle) and an example of the modular maze structure with gangways and choice points (right). **B**. The main performance metric is normalized path ($path_{norm}$) with the length of the paths taken by the animal divided by the shortest possible path to the goal location. **C.** During training animals started each trial from a different location and had to navigate to a fixed goal location. **D**. Animals were trained in three sessions a week, with each mouse running as many trials as possible in 30min. Animals were run in sequence. **E.** Shows the general training schedule for the whole experiment. During Build-up animals were trained to one of five goal location in a given session. The goal location was kept constant for 7 sessions in the first repeat (R1), then 6 in R2, and for R3-5 each 5 session. During Reinforcement 3 of the initial 5 locations were repeated with each R containing 3 sessions. Finally during the Updates each repeat also contained 3 sessions. Updates were performed as new goal locations, inclusion of new barriers or the inclusion of both. The sequence of the update sessions was counterbalanced across animals. Each Update type was repeated 3 times. Throughout all 3 phases the first trial of the second session and during Build-Up in R1 S7, R2 S5, R3-5 S5 was performed as probe trial without any food present to control for any confounding effects of smell.

Results

Build-Up

Only sessions 1-5 were included in the statistical analysis for a complete model. Within subject analysis showed a significant effect of Repeat ($F_{4,28}$=4.3;p=0.008) and Session ($F_{4,28}$=7.9;p<0.001) but no interaction ($F_{16,112}$=0.9;p=0.61). For both Repeat and Session the linear contrast was significant (R p=0.011, S p=0.013) indicating that performance in general increased across session (learning how to navigate to a goal location) as well as across the five repeats (new goal locations are learned faster).

To determine if performance increased within a session or overnight, we subdivided the first three sessions into trial blocks (1-8, 9-16, 17-24). Within subject analysis showed a significant effect of Trial Block ($F_{2,12}$=8.4;p=0.005), Session ($F_{2,12}$=21.4;p<0.001) and SessionXTrial Block interaction ($F_{4,24}$=2.8;p=0.046) but no effect of Repeat ($F_{4,24}$=1.8;p=0.17) or other interactions (all F<1.1;p>0.3). For both Trial Block and Session the linear contrast was significant (TB p<0.001, S p=0.001).

The performance on the first trial of each session measures long-term memory (48-72h) in contrast to the whole session performance. Focussing on this trial within subject analysis showed a significant effect of Session ($F_{4,28}$=2.9;p=0.04) but no effect of Repeat ($F_{4,28}$=0.2;p=0.94) or interaction ($F_{16,112}$=1.1;p=0.41).

Reinforcement

Within subject analysis showed a significant effect of Session ($F_{2,14}$=7.7;p=0.006) and marginal significant for Repeat ($F_{2,14}$=3.4;p=0.062) but no interaction ($F_{4,28}$=1.7;p=0.16). For Session the linear contrast was significant (S p=0.006) indicating that performance in general increased across session .

Trial blocks (1-8, 9-16, 17-24) analysis showed a significant effect of Trial Block ($F_{2,12}$=5.1;p=0.024), Session ($F_{2,12}$=21.2;p<0.001), Repeat ($F_{2,12}$=5.4;p=0.021) and marginal significant SessionXRepeatXTrial Block interaction ($F_{8,48}$=2.0;p=0.067) but no other interactions (all F<0.8;p>0.5).

The performance on the first trial of each session measures long-term memory (48-72h) in contrast to the whole session performance. Focussing on this trial within subject analysis showed only a marginal significant effect of Session ($F_{2,14}$=3.1;p=0.075) but no effect of Repeat ($F_{2,14}$0.4;p=0.67) or interaction ($F_{4,28}$=1.2;p=0.33).

Updates

Within subject analysis showed a significant effect of Session ($F_{2,14}$=17.9;p<0.001) and marginal significant effect of Type ($F_{2,14}$=3.3;p=0.068) but no interaction ($F_{4,28}$=1.1;p=0.39). For both Type (marginal) and Session the linear contrast was significant (T p=0.097, S p<0.001) indicating that performance in general increased across session (learning how to navigate to a goal location). Just considering the first session performance a significant type effect was seen ($F_{2,14}$=5.3;p=0.019) indicating that how much new information needs to be integrated into the existing map (just barrier, new location or both) affects within session, online learning.

Again, Trial block (1-8, 9-16, 17-24) analysis showed a significant effect of Session ($F_{2,14}$=23.9;p<0.001) but no effect of Type ($F_{2,14}$=2.3;p=0.14), Trial Block ($F_{2,14}$=1.0;p=0.4) or interactions (all F<1.3;p>0.3). For Session the linear contrast was significant (p<0.001), indicating an increase in performance across sessions.

The performance on the first trial of each session measures long-term memory (48-72h) in contrast to the whole session performance. Focussing on this trial within subject analysis showed a significant effect of Session ($F_{2,14}$=5.8;p=0.014) but no effect of Type ($F_{2,14}$=1.1;p=0.34) or interaction ($F_{16,112}$=0.9;p=0.47). For Session the linear

contrast was significant (p=0.005) indicating that performance in general increased across session (long-term memory performance).

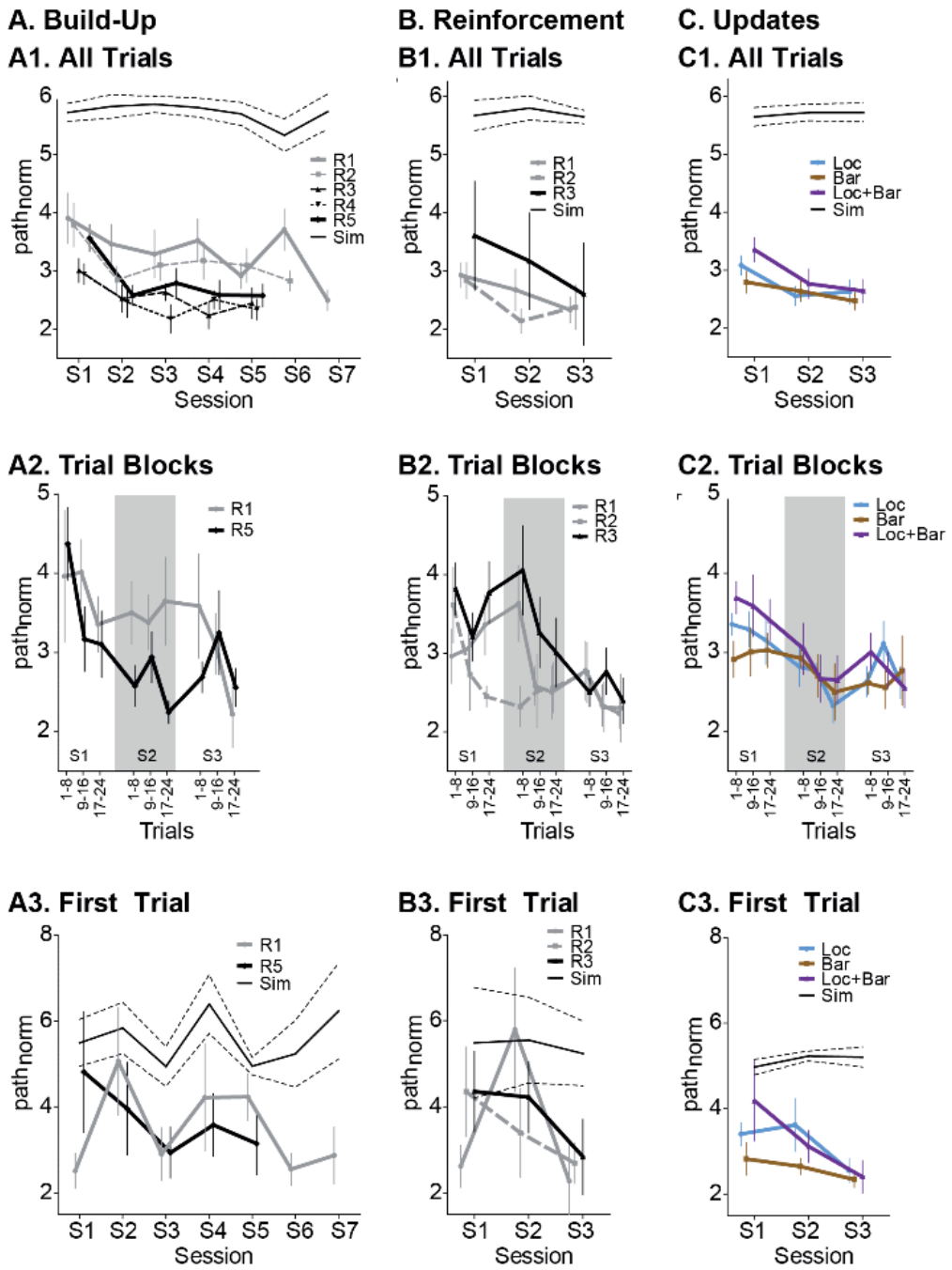

Fig. 2 Hex-Maze Performance: Column A. shows the Build-up phase**, B**. the Reinforcement and **C**. the Updates (Location, Barrier, and Location + Barrier). **Row 1**. Shows session (**S**) performance (averaged across all trials) for each repeat (**R**) in each phase, **row 2**. Only shows the first three sessions in each phase, but then depicts averages for trial blocks (1-8, 9-16, 17-24), and **row 3** the first trials of each session as long-term memory measure; in contrast sessions averages as in row 1 and 2 are more likely to reflect short-term or working memory. **Sim**=simulated data to estimate chance level.

Previous Knowledge Effects

Different effect of previous knowledge could be observed in the data. The simplest effect is already seen in the first Repeat in Build-Up, in which a significant session effect indications that each session benefits from the previous experience of the previous session ($F_{6,42}$=3.2;p=0.012, Fig. 3A). This simple learning effect while often not considered as previous knowledge effect, does affect session performance and thus must be considered even in experiments, which just focus on such session as seen in most electrophysiological experiments.

The second previous knowledge effect is how fast a new goal location could be incorporated into the existing map, tested at every goal location switch from Build-Up to Updates. Such a full model (only with the first three sessions of each phase, and Build-Up 3-5 as well as Reinforcement and Updates averages across repeats) showed a significant phase effect ($F_{1,14}$=6.8;p=0.02, Fig. 3B). This is reminiscent of a learning set effect.

To test the schema effect – speeding up consolidation of long-term memories – we compared the first trial performance across the first three session of the Build-Up and Reinforcement phase to the Updates. A significant session effect ($F_{4,28}$=10.1;p<0.001) as well as a significant difference of phase was seen ($F_{1,14}$=6.0;p=0.028, Fig. 3C). More specifically, follow up t-tests only showed a significant difference between the phases for session 2 (t_7=2.8;p=0.015, Bonferroni adjusted threshold p<0.016) but not S1 (t_7=1.2;p=0.25) or S3 (t_7=0.8;p=0.4) indicating that long-term memory expression was accelerated across phases from 2 session learning to 1 session learning.

Finally, when considering the amount of information that needed to be incorporated in the Updates and focussing on only the first session to test online encoding effect, a significant effect of type was seen ($F_{2,14}$=5.3;p=0.019) indicating that how much new information needs to be integrated into the existing map (just barrier, new location or both) affects within session, online learning (Fig. 3D).

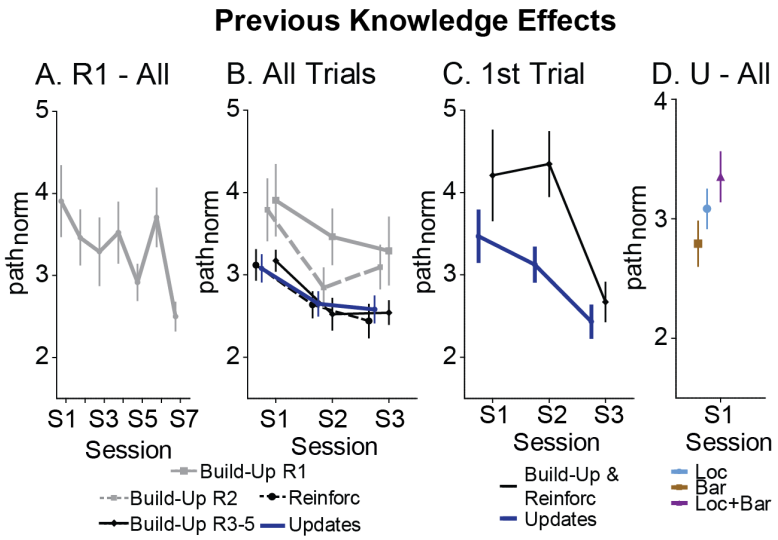

Fig. 3 Previous Knowledge effects: A. shows the whole session performance for the first goal location in training. As seen by the significant session effect (p=0.012), performance increases across experience indicating more efficient short-term or working memory. **B.** plots performance for the first three sessions of the Build-Up repeats, as well as Reinforcement and Updates phase. Already by the second repeat a significant increase in performance is seen in S2 across the whole session. This performance increase is seen overnight (see also Fig. 2. A.2) and may represent more efficient consolidation and updating but is only expressed in the whole session average (not long-term memory in the first trial, see Fig. 2. A and B 3). This is reminiscent of a learning-set effect. In contrast, **C.** shows the performance of only the first trial and here during Build-up no long-term memory (48-72h) is seen (stable performance across S1 and S2). However, once a schema is established one session training leads to faster long-term memory and a one-session learning effect for 48h memory (S2 Build-Up/Reinforcement vs Updates p=0.015). First trial of S2 was run as a probe trial w/o food. **D.** A final previous knowledge effect is depicted in this panel. Focussing on the first session of the Updates a significant types effect was seen (p=0.019). The barrier, goal location and combined updates differed in their overlap with previous knowledge (or need for updating that knowledge), which influenced how rapidly they improved short-term or working memory performance in the first session. Of note, in D y axis adjusted for better visualization of difference (in comparison to A-C).

Discussion

In the present study we aimed at developing a new rodent task that enables the investigation of previous knowledge on memory encoding and consolidation. With the Hex Maze different aspects on how previous knowledge affects performance and learning could be seen ranging from simple day-to-day increase on performance, to learning-set and schema effects on offline consolidation and online learning. This data shows that this task can flexible be used in memory research while controlling for difficulty of learning across each phase in training: from Build-Up of knowledge to memory updates.

Most rodent memory research assumes that the animal is naïve to the learned material, which stands in contrast to naturalistic learning, in which learning rarely occurs in isolation of previous experience once subjects have reached adulthood. This difference may be contributing to translation failures when applying knowledge gained in animal research to human subjects. Previous knowledge will affect behaviour and learning and thus needs to be considered when applying any particular training paradigm. To test these effects, here we used a spatial environment that is large and more naturalistic in its complexity. Mice were trained to find food from different starting locations, enabling allocentric learning, to one fixed food location per session over three training phases: Build-Up (Session 1-28), Reinforcement (session 29-38) and Updates (session 39-66). During Build-Up the goal location was kept constant for 5-7 sessions before switching to a new one, while in Reinforcement (repeating goal locations from the Build-Up) and Updates switches occurred every 3 sessions. Three different types of updates were performed in this final phase: changing the goal location, including barriers blocking certain paths and the inclusion of both new goal location as well as new barrier locations. Across all phases memory effects could be seen, with performance measured by normalized path length increasing from one session to the next. Further, four distinct effects of previous knowledge on performance and learning could be seen.

The most simple and obvious previous knowledge (or memory) effect is already seen in the first few sessions of the Build-Up phase, in which navigation to the goal location (in this case constant) becomes more efficient from one day to the next. This simple memory effect is what most rodent memory task would capture, e.g. using a radial-arm maze (Jarrard 1995) or watermaze testing reference memory (Morris et al. 1982). While one could argue if this simple memory effect is a “previous knowledge” effect, it is important to consider it as its simplest form: the knowledge of previous training days affects performance the next day.

The second previous knowledge effect can be seen when comparing the very first goal location performance to the second and other goal location switches. Already the second goal location shows a faster learning curve across sessions in comparison to the very first. This is reminiscent of the Learning Set Effect (Harlow 1949), which describes the phenomena that you need to *learn how to learn efficiently.*

The third previous knowledge effect is seen in long-term memory performance (first trial of each session). Initially, during the Build-Up and Reinforcement phases the animals do not show long-term (48-72h) memory until the third session (so after two sessions of training), however during the Update phase the development of long-term memory is accelerated and now can already be seen on session 2 so after only one session of training. This acceleration of consolidation has previously been linked to the schema effect. Using a paired-associated task (flavor-locations) it has been shown that such a schema will allow systems consolidation (and thus hippocampal independency) to occur within 24-48h instead of weeks to months (Tse, Langston et al. 2007). Further, they could identify that both hippocampus and the prefrontal cortex were critical for rapid updating to occur (Bethus, Tse et al. 2010; Tse, Takeuchi et al. 2011; Wang, Tse et al. 2012). These findings were later replicated in human subjects (van Kesteren, Fernandez et al. 2010; van Kesteren, Rijpkema et al. 2010; van Buuren, Kroes et al. 2014; Wagner et al. 2015). Recently Ghosh and Gilboa (2014) summarized four key features of schemas: (1) an associative network structure, (2) basis on multiple episodes, (3) lack of unit detail, and (4) adaptability. All for requirements are present in our task

in which we aim to test a spatial schema or map: the extra- and intra-maze cues together with the maze-layout represent the associate network structure, training takes multiple sessions or episodes and we have shown adaptability in the update phases. Solely the lack of unit detail is hard to assess in this context. One criticism in schema tasks, is that usually pre-training on the schema and the updates differ in difficulty and cognitive load (Tse, Langston et al. 2007; van Buuren, Kroes et al. 2014), which could account for the rapid updating effect. The advantage of present paradigm is that here this is not the case, both the Build-Up and Update consist of one goal location so the difficulty remained the same.

The fourth previous knowledge effect could be seen across the different types of Updates: the amount of new information that needed to be incorporated into the schema affected how rapid online learning could occur during the first session of each update. If only general maze structure was changed (inclusion of barriers) the animals could adapt their routes rapidly and additional sessions were not needed to reach optimal performance, in contrast if additionally the goal location was changed or both the goal location and maze structure (loc+bar) online learning was slower resulting in worse performance during the first session. However, offline consolidation eliminated this effect and by the second session animals performed the same in all types of updates. This effect that the degree of change in comparison to the previous learned information affected online learning and thus perhaps initial recruitment of brain structures could explain some differences in schema effects in past rodent and human work. In the original pared-associate task the hippocampus was necessary during encoding of the updates, and this hippocampal involvement was also observed in a similar human schema task that tested a recently acquired, simple schema (card-location associations) (van Buuren, Kroes et al. 2014). In contrast, human schema tasks that involve long-established, real-world schemas the hippocampus tends to not be active, instead the prefrontal cortex directly communicates with the other cortical regions. It would be tempting to speculate that there may be a gradient across the complexity or extent of the existing schema that in combination with the amount of overlap new information has with such a schema results in a shift from hippocampal to cortical involvement. (1) If no schema is present the hippocampus is necessary for weeks to months, (2) if a simple schema is present the hippocampus is necessary for memory encoding but new information becomes hippocampal independent faster and (3) if a complex schema is present the hippocampus is not even necessary for encoding, which can be also seen in the case of fast-mapping (Coutanche et al. 2014; Coutanche et al. 2015).

In sum, with the Hex-Maze we have developed a flexible rodent task in which different effects of previous knowledge on memory performance, encoding and updating can be investigated. This will enable future studies investigating how memory updating occurs and which mechanisms are involved. While we have not yet tested if the schema effect of rapid systems consolidation is present in this task as well, we do show a behavioral schema affect that is likely to be accompanied by the consolidation effect. Overall, our brains are tuned to remember things that are new, but how novel something is will depend on what you have experienced (Duszkiewicz et al. in press).

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