The Object Space Task for mice and rats

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ABSTRACT
An important aspect of a memory is whether it is representing a specific event or whether it is a representation of knowledge extracted over multiple episodes. To investigate this difference, we developed a new multi-trial behavioral task that can assess memory accumulation in rodents. It makes use of rodents' innate drive to explore novelty and allows for later recordings (e.g. electrophysiology) and interventions. The task consists of three distinct conditions (*stable*, *overlapping, random*) that can be repeated within animals. Rodents are exposed to multiple sample trials, in which they explore objects in specific spatial arrangements. In the *stable* condition, the locations are constant during all sample trials, and one object's location changes during test. In the *random* condition, object locations are presented without a specific spatial pattern. In the *overlapping* condition, one location is shared (overlapping) between all trials while the other location changes during sample trials. We show that in the *overlapping* condition, instead of only remembering the last sample trial, rodents form a cumulative memory of the sample trials.
We adapted the task so that it can be learned by both rats and mice, making it suitable for investigating this aspect of memory across species and using a wide array of methods to measure and perturb the neural basis of memory.

INTRODUCTION

Multiple tasks and behavioral tools have been developed to study memory processes in rodents. By varying aspects of the task, for example the chosen motivator or the amount of training trials, different aspects of memory mechanisms can be studied. Memories are stored and retrieved in different ways, depending for example on the age of memory and the character of memorized information. Episodic memory retains the details of the memorized event. Conversely, semantic memory pertains to general knowledge that is extracted cumulatively across multiple events. Memory consolidation processes may promote the transformation between these two types of memory organization (Frankland and Bontempi 2005; Moscovitch, Cabeza et al. 2016). However, many tasks, especially for rodent subjects, cannot differentiate between the two.

Paradigms that can be trained in a short time (1-2 sessions) are widely in use, because they enable one to determine exact timings of memory interventions. But many such protocols require the animal to experience aversive events, such as electrical shocks in fear conditioning or avoidance learning (Maren 2001; Tovote, Fadok et al. 2015), or other strong motivators such as water or food reward are employed. Such learning incentives activate the neuromodulatory systems, a fact often not considered in studies using these tasks (Martin-Soelch, Linthicum et al. 2007). Neuromodulation is known to have a major effect on the memory system (Redondo and Morris 2011; Takeuchi, Duszkiewicz et al. 2016; Genzel, Rossato et al. 2017). Therefore, this makes these tasks difficult to compare with most, more neutral paradigms used in human research. In contrast, object recognition paradigms make use of a rodent's natural tendency to explore novelty, thus allowing for the investigation of memory processes without an intrinsic, difficult to control, side effect on the motivation, emotion and the neuromodulatory system (Ennaceur and Delacour 1988; Ennaceur, Neave et al. 1997; Warburton and Brown 2015).

Another critical factor determining influencing memory acquisition is the frequency of events the animal experiences. In some memory tasks, the animal is exposed to repeated training trials. Spatial memory tasks such as the watermaze consist of multiple sample trials for the rodent to learn the location of a hidden platform most commonly trained across multiple days (Morris 1984). The radial arm maze requires animals to repeatedly sample baited arms and their memory performance is assessed by the number of errors, namely the frequency of unbaited arm visits within a given trial; again, days to weeks of training are needed for the animal to perform above chance level (Olton 1987; Bontempi, Laurent-Demir et al. 1999). Similarly, in some aversive conditioning paradigms, subjects undergo multiple pairings of a conditioned stimulus (CS) such as a tone or light with a mild foot shock (Tovote, Fadok et al. 2015). In other memory tasks, the animal only experiences a single event, which is the case in some fear memory paradigms, object recognition or object displacement memory (Okuda, Roozendaal et al. 2004; Bermudez-Rattoni, Okuda et al. 2005; Beldjoud, Barsegyan et al. 2015). In object tasks, animals are allowed to explore two objects in a given environment for certain amount of time. After a delay, a short delay to assess short term memory or a delay of 24 hours to assess long-term memory, one of the objects is either replaced by a novel object (object recognition) or moved to a novel location (object displacement memory). Memory is assessed by calculating the difference in exploration time of the (for rodents preferred) novel item versus the familiar. In tasks where the amount of events the animal experiences varies greatly, it is unclear which part of the training was significant to the animal's performance. Is only the most recent event memorized by the animal? Or can memory be accumulated across extensive time periods or multiple trials?

These questions are key to understanding mechanisms of episodic vs. semantic memory, but they are difficult to address in most memory tasks. However, some recent work has attempted to study the accumulation of evidence across multiple events. An example is a modified version of the watermaze, in which evidence accumulation was assessed as mice were trained on multiple platform locations that were drawn stochastically from a specific spatial distribution and retrieval of 'averaged' memory of the learned platform locations was assessed after a 1-day or 30-day delay (Richards, Xia et al. 2014). Another example is paired-associate learning in rodents, in which memory of flavor-place associations is gradually learned with repeated trials (Tse, Langston et al. 2007; Tse, Takeuchi et al. 2011; Wang, Tse et al. 2012).

Training procedures in these cumulative memory tasks are often lengthy and labor-intensive. In addition, information can be mainly acquired from either retrieval and/or updating: encoding and consolidation processes are difficult to study. A water-based paradigm such as that of Richards et al (Richards, Xia et al. 2014), is ill-suited for electrophysiological recording of brain activity during learning. We overcame these limitations by developing a task designed to extract information from multiple, similar events accompanied by suitable control conditions. For this we employ a rodent's natural tendency to explore novelty in the presence of familiarity to our advantage in a new object location task with different conditions varying in degree of stable and variable information across trials, the *object space* task. We developed task versions that are suitable for both rats and mice.

In this new *object space* task, rodents are allowed to explore two objects in different across-trials patterns, presented in a *stable, overlapping* or *random* configuration. In the *stable* condition, objects are always presented in the same location across sample trials (see figure 2 and 3). In the test trial, after a delay, one object is moved to a novel location. We expect to see a preference for the object in the novel location in the test trial but no preference for either location over the course of training. This condition can be solved by remembering only the final sample trial (that is, using episodic memory) or by creating a cumulative memory of all sample trials. The *overlapping* condition is our key condition. One object location remains stable across sample trials whereas the other object moves between one of three locations each sample trial. The key here is that the last sample trial shows the same configuration as the test trial after a delay. Thus, if the animal only remembers the most recent event it experienced, it will show no preference for either object location since both locations are familiar to the animal. Conversely, if the animal has accumulated the overlapping information of the stable location over time, it will still show a preference for the location less often shown. The *random* condition consists of objects presented in random spatial configurations in which no patterns can be extracted and no place preference should develop.

The three conditions can be repeated multiple times in the same animals, thereby allowing for within-subject designs. Secondly, it is easy to combine behavioural training with physiological measures such as electrophysiology and other manipulations. The rat version of this task requires only one day of training involving 5 trials with 50min inter-trial intervals, a 10min test trial follows 24hrs later. In mice, this training protocol is repeated over the course of 4 days and a test trial follows 24hrs after the fourth training day. We show here that both rats and mice by default remember a cumulative memory.

METHODS

Subjects

Male C57Bl6/J mice, 7-8 weeks of age at the start of behavioral training (Charles River) and male Lister Hooded rats (12 weeks, Charles River) were group housed with *ad libitum* access to food and water. Animals were maintained on a 12h light/dark cycle and tested during the light period. In compliance with Dutch law and Institutional regulations, all animal procedures were approved by the Central Commissie Dierproeven (CCD) and conducted in accordance with the Experiments on Animal Act.

Behavioral training

Habituation

Animals were thoroughly handled in their second week after arrival in the animal facility. Each animal was handled daily for at least 5 minutes. We emphasize here that handling of the animals is extremely important. Picking them up by the tail is aversive and inadequate handling can affect the animal's performance on multiple tasks (Gouveia and Hurst 2016). Mice and rats were handled so that they typically climbed by themselves on the experimenter's hands when taking them out of the home cage and out of the training arena. After handling, animals were habituated to a square arena (75cmx75cm) for 5 sessions within 5 days. The walls and the floor were white or green to facilitate background subtraction in video analysis software. On the bottom side of the floor, magnets were placed in 4 locations for easy and consistent placement of the objects; objects were affixed to square metal plates (Fig 1). In the first session, the animals were allowed to explore the box together with all cage mates for 30 minutes. In the second and third session, they were placed in the box individually for 10 minutes. In the final two sessions of habituation, two objects (towers made from Duplo blocks, not used in main experiment) were placed in the box and the animals were allowed to explore for 10 minutes.

Training

The object space task consists of three conditions: stable, overlapping and random as described above (see Fig 2, 3). Conditions and locations were counterbalanced among animals and sessions and the experimenter was blinded to the condition. At the beginning of each session (2 days for rats, 5 days for mice), cues were placed on the walls inside the box and at least one 3D cue was placed above one of the other walls. Cue distribution was intentionally non-symmetric. A camera was placed above the box to record every trial and to allow for online scoring of exploration time.

In each condition, animals were allowed to explore two objects for 5 minutes with an inter-trial interval of 30min for mice, 50min for rats. Mice were trained interleaved in groups of 4 with two groups per day (morning/afternoon), rats in groups of 8 (one group per day). Before the beginning of each sample trial, the box and the objects were thoroughly cleaned with 70% ethanol. Each sample trial consisted of a different pair of matching objects varying in height width, texture and material (including metal, glass, plastic and wood, see figure 1 for example objects). Object sizes ranged from 4-26cm in height to 5-18cm in width. Objects were glued onto metal coasters and placed onto the magnets that were fixed on the floor of the arena.
Objects were never repeated during the training period of one condition (1 session). Rats received 5 sample trials in total. This procedure was repeated in mice over the course of 4 consecutive days in which they were presented with either 3 sample trials per day or 5 sample

trials per day, thus accumulating in 12 or 20 total sample trials. The test trial, 24hrs after the last sample trial, consisted of again two objects and animals were allowed to explore for 10 minutes, however only the initial 5 min were used.

Data acquisition

We developed an in-house program for training and scoring. The Object Scorer reads in previously prepared training sheets with the object and locations for each trial of each animal, presents this information at the beginning of each trial to the experimenter (see Fig 1) and automatically extracts exploration times from the manually-scored videos. Therefore, the operator cannot keep track of which animal is in which condition, and which are the stable vs. moved object for each trial, and he or she can be considered blind. Source code for the Object Scorer software is available at https://github.com/MemDynLab/obj_scorer.

Statistical analysis

The discrimination index (DI) used to assess memory performance was calculated as the difference in time exploring the novel object location and stable location divided by the total exploration time. This results in a score ranging from -1 (preference for the stable location) to +1 (preference for the moving object location). A score of 0 indicates no preference for either object location. Total exploration time and discrimination index were assessed with MANOVAs with factors condition and trial/day. One sample t-tests were performed to analyze memory performance to chance level in the last sample trial and test trial.

Figure 1 Object Space Task Materials:
Examples of objects used in the object space task. Objects vary in size, width, texture and material. Objects were placed in two of the four corners. On the right: example of the object scorer program with pop-up pre-trial (top) and with scoring (bottom).

RESULTS

Mouse training: 3 sample trials per day

Initially, we trained mice (n=7) with 3x 5min sample trials per day for each condition (Fig 2, left). Exploration time of animals over the course of training was not significantly different between conditions but did show a significant trial effect (condition $F_{2,12}$=0.8, p=0.47; trial $F_{12,72}$=14.3, p<0.001; conditionXtrial $F_{24,144}$=0.56, p=0.95). Discrimination index averaged for each day showed a significant effect of condition (condition $F_{2,12}$=6.2, p=0.014, day $F_{4,24}$=0.84, p=0.51; conditionXday $F_{8,48}$=0.6, p=0.78). Focusing on the final training and test trial, again a significant effect of condition was found (condition $F_{2,12}$=4.6, p=0.033, trial $F_{1,6}$=1.75, p=0.23; conditionXtrial $F_{2,12}$=1.3, p=0.31). Performance in the *overlapping* condition was above chance at the final sample trial but not at the test trial (final training trial: t_6=4.2, p=0.006; test trial: t_6=1.2, p=0.27), Furthermore since we did not observe even a numerical effect on the *stable* condition (final training trial: t_6=0.6, p=0.57; test trial: t_6=-1.5, p=0.18, *random* final training trial: t_6=-1.6, p=0.16; test trial: t_6=-0.1, p=0.99), indicating that there was no 24hr long-term memory effect after training. Together these results suggest that more extensive training is needed for mouse subjects, therefore we chose to train the mice on 5 sample trials per day instead of 3.

Mouse training: 5 sample trials per day

The 5-trial a day version was performed once with the original batch of seven animals which previously run the 3 trials-per-day version, and then repeated with another 8 animals (total n=15). With 5 sample trials per day, no differences in total exploration time were found between conditions but a significant trial effect was again seen (condition $F_{2,28}$=0.06, p=0.94; trial $F_{20,280}$=4.8, p<0.001; conditionXtrial $F_{40,560}$=0.49, p=0.99, Fig 2). Discrimination Index across days showed a significant conditionXday interaction (condition $F_{2,28}$=0.2, p=0.81, day $F_{4,56}$=1.7, p=0.17; conditionXday $F_{8,112}$=3.16, p=0.003). And concerning the final training and test trial, there was also a marginal significant condition effect and trial x condition interaction (condition $F_{2,28}$=2.7, p=0.085, trial $F_{1,14}$=0.4, p=0.55; conditionXtrial $F_{2,28}$=2.86, p=0.074). Additional one sample t-tests indicated an increased memory performance above chance for the stable condition in trial 21 (t_{14}=2.5, p=0.026) but not in trial 20 (t_{14}=-0.8, p=0.44). Importantly, memory performance on trial 20 in the overlapping condition is significantly above chance (t_{14}=2.4, p=0.034) and a trend was observed in trial 21 (t_{14}=2.0, p=0.07). Finally, no significant effects were observed in the random condition (final training trial: t_{14}=0.8, p=0.43; test trial: t_{14}=-0.7, p=0.51).

Rat training: 2-day training paradigm

Rats were only trained for 5 trials in one day before being retested 24h later (Fig 3). There was no significant condition or trial effect on total exploration time (condition $F_{2,28}$=0.3, p=0.76; trial $F_{5,70}$=1.4, p=0.25; conditionXtrial $F_{10,140}$=0.6, p=0.68). The DI across all 6 trials showed no significant condition or trial effect (condition $F_{2,28}$=0.6, p=0.55; trial $F_{5,70}$=1.1, p=0.36; conditionXtrial $F_{10,140}$=1.54, p=0.13). However, when focusing on the final test trial, there was a significant condition effect (condition $F_{2,28}$=7.0, p=0.003). Further, only DI for the overlapping and the stable condition were significantly above chance (overlapping: t_{14}=2.5, p=0.025; stable: t_{14}=2.2, p=0.044), in contrast the random was marginally below chance level (t_{14}=-1.9, p=0.067).

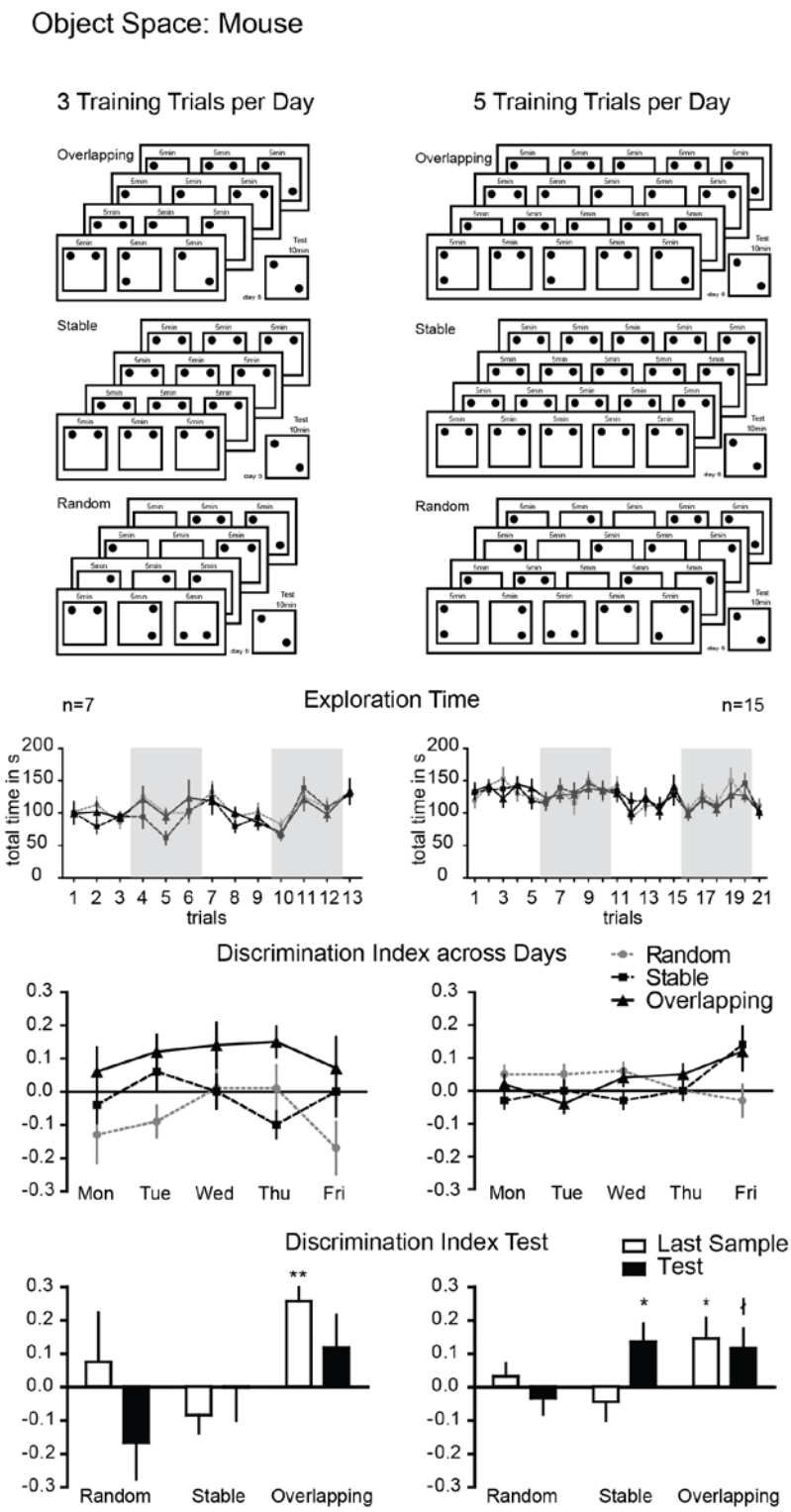

Fig 2 Object Space Task Mouse:
1.Panel: Trial structures for the three different conditions. In the *overlapping* condition, one location remains constant across all sample trials and the test trial, the second location varies. The locations in the last sample trial and in the test trial are equal. In the *stable* condition, the locations remain the same in all sample trials and one object is displaced in the test trial. In the *random* condition, the locations were pseudo-randomly chosen to not allow extraction spatial patterns. One session consisted of 5 sample trials for 4 subsequent days and test trial 24hrs later. 2. Panel: Exploration time in 3 trials (left) versus 5 trials (right). The total exploration time per trial remained constant across conditions and sample and test trials in both 3 trials and 5 trials per day. 3. Panel: Discrimination Index (for statistical details see main text). The DI averaged for each training day showed a significant effect of condition for the 3-trial and condition x trial interaction effect in in the 5-trial paradigms. 4. Panel: DI at the final training trial and test trial. In the 3 trial paradigm (left), performance in the overlapping condition was above chance at the final sample trial but not at the test trial. We did not find such effect for the stable or random condition. With 5 trials per day (right), performance was significantly above chance level in the overlapping condition for trial 20 and a significant trend at trial 21. In the stable condition, only trial 21 showed a significant effect. No significant effects are observed in the random condition.

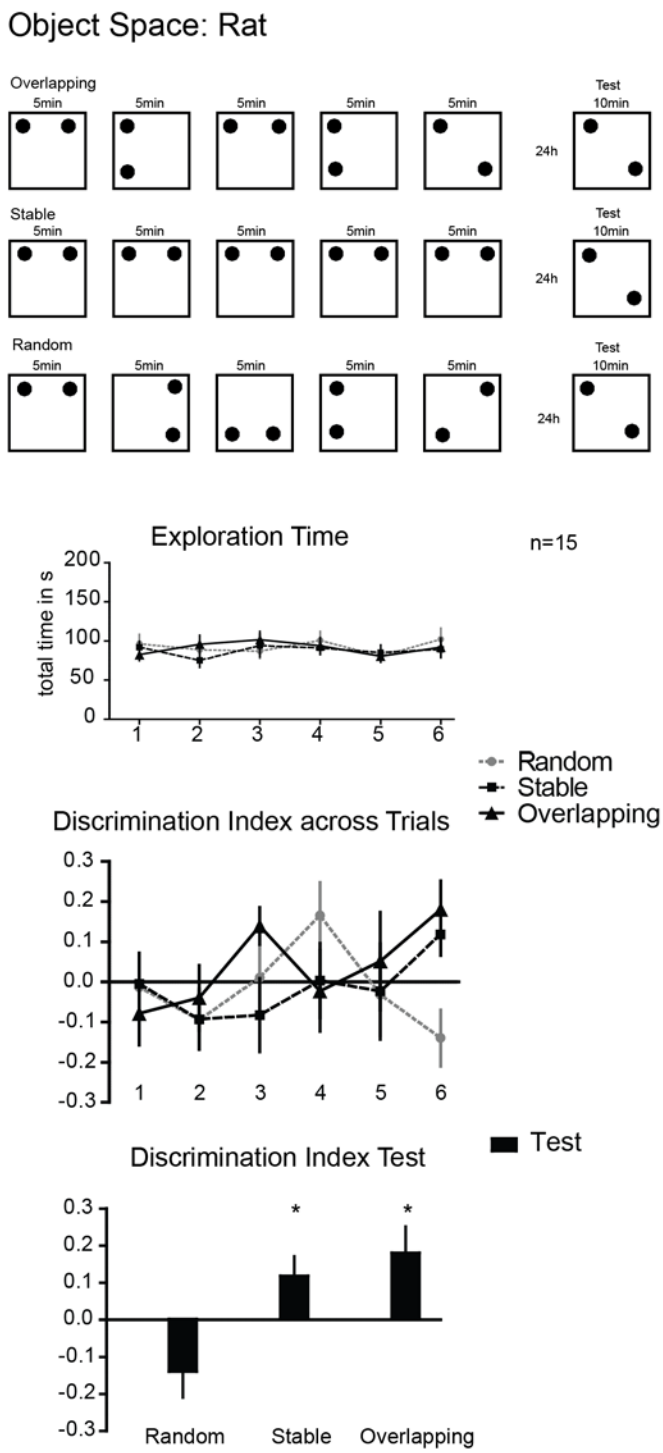

Fig 3 Object Space Task Rat:
1. Panel: Trial structures for the three different conditions. In the *overlapping* condition, one location remains constant across all sample trials and the test trial, the second location varies. The locations in the last sample trial and in the test trial are equal. In the *stable* condition, the locations remain the same in all sample trials and one object is displaced in the test trial. In the *random* condition, the locations were pseudo-randomly chosen to not allow extraction spatial patterns. One session consisted of 5 sample trials on one day and a test trial 24hrs later. 2. Panel: Exploration time. The total exploration time per trial remained constant across conditions and sample (1-5) and test (6) trials. 3. And 4. Panel: Discrimination Index (for statistical details see main text). The DI across sample and test trials did not show a significant condition or trial effect. In the test trial, there was a significant condition effect and the DI was significantly positive only for stable and overlapping condition.

DISCUSSION

Memory accumulation is a gradual process that requires the experience of multiple, similar (or overlapping) events, in contrast episodic memory is by definition based on one event (Wang and Morris 2010; Moscovitch, Cabeza et al. 2016). Although several tasks have been developed to study cumulative memory, we attempted to develop a task that is simple and easy to implement, that allows for a time-saving within-subjects design and makes use of a rodent's natural behavior without any external motivators. We have successfully demonstrated that the *object space task* can be used as a task for cumulative memory and contains a control condition that can be solved with a single event memory. By the end of training, both rats and mice show cumulative memory in the *overlapping* condition, indicated by a positive DI in the test trial. Performance in the *stable* condition is, as expected, increased only in the test trial. Finally, object locations in the *random* condition were treated without preference by the animals.

Because the same configuration is used as in the last training trial, the test trial provides a control for any recent memory-like effects in our *overlapping* condition, clarifying whether the animal has accumulated memory over the course of learning instead of using their most recent experience to guide their behavior. If the animal shows no preference for either object location at the test trial, it can mean two things. Either the animal is only remembering its most recent experience or the animal has not acquired any (long-term memory). The *stable* condition does help to differentiate these two effects, since if the animal can retain a memory of the most recent experience but not a cumulative memory it still will be above chance in this condition. Thus all three conditions together (*overlapping*, *stable* and *random*) enables us to test if an animal under current conditions can remember an event and/or a cumulative memory.

In our 3-trial mouse paradigm, the mice did not show memory in the *stable* condition during the test trial. However, in the 5-trial paradigm we did find memory in the *stable* condition. Interestingly, in both paradigms mice seemed to be able to accumulate overlapping information. 3 sample trials per day equals to 3x 5min of training. Our results indicate that this was not enough for the animals to reliably retain the memory for 24hours, which is why we focus the subsequent work on 5 trials per day. The major difference between the *overlapping* condition and the *stable* condition has to do with novelty. Moving one object to a different location within each sample trial most likely triggers the animal's attention, thereby facilitating learning. In the *stable* condition on the other hand, the presence of objects in fixed locations across trials is less likely to prompt attention with each sample trial, hence more repeated events are required for the animal to learn.

While mice require multiple sample trials across multiple days to acquire cumulative memory in this task, rats require just one day of training consisting of 5 sample trials in total. Despite this difference in training duration and the definite slower learning curve in mice, we see it as an advantage that this task can be used in both rodent types. Several studies have compared performance in various (complex) tasks in rats and mice and often concluded that mice cannot perform as well as rats (Whishaw and Tomie 1996; Cressant, Besson et al. 2007; Carandini and Churchland 2013). However, as we show in our task, by adapting the protocol mice are able learn this task, thereby expanding the opportunities for the use of this task in numerous animal models. Despite these differences in training duration, we expect that learning in this task underlies similar mechanisms in both rats and mice. However, we cannot draw any conclusions on this until further research has been conducted.

In addition to adapting the task to rats and mice, we developed a software to track the exploration behavior and allow for online scoring of exploration periods. The program automatically reads in pre-defined trial structures and only informs the experimenter about the objects and locations used right before each trial. Combining this approach with interleaved testing of several animals during one experimental session, we effectively blind the experimenter with respect to the condition in the current trial and therefore enable them to score exploration behavior without introducing an experimenter bias.
In the future, this task will allow for the investigation of the neural circuits contributing to cumulative and event memory. This task is especially suitable for this as memory conditions tapping into memory accumulation vs. event memory can be presented in the same spatial layout and with very similar overall behavior, as indicated by the lack of difference in total exploration time across conditions.
Previous studies have provided evidence that the hippocampus is more involved in the processing of recent experiences that include episodic details, whereas the prefrontal cortex accumulates information from multiple, similar experiences, thereby creating a more stable but also more generalized memory over time (Frankland and Bontempi 2005; Tse, Takeuchi et al. 2011; Wang, Tse et al. 2012; Preston and Eichenbaum 2013). We can hypothesize that successful performance on the overlapping condition involves the integration of multiple or all events in the prefrontal cortex, thereby creating a stable representation of the overlapping object location in space. While the classic version of our stable condition, namely 24h-object-displacement memory, is usually described as a hippocampal-dependent task (Mumby, Gaskin et al. 2002; Assini, Duzzioni et al. 2009; Haettig, Stefanko et al. 2011; Haettig, Sun et al. 2013), we cannot assume that our stable condition is also dependent on the hippocampus. Object-displacement memory requires the animal to experience only one event, in the object space task the animal experiences multiple events of the same spatial configuration. Thus, the animal can solve this task by using both its most recent experience and the cumulative memory of the events.

In conclusion, the object space task can be used to study cumulative memory in both rats and mice. Rats require one day of training to acquire a cumulative memory while mice require multiple days of training in order to learn this task. Although we can speculate about a critical role of both prefrontal cortex and hippocampus to acquire cumulative memory in the object space task for both rodent types, the neural mechanisms underlying memory performance should be determined next.

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