



## Hippocampal activation during the recall of remote spatial memories in radial maze tasks



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### ABSTRACT

Temporally graded retrograde amnesia is observed in human patients with medial temporal lobe lesions as well as in animal models of medial temporal lobe lesions. A time-limited role for these structures in memory recall has also been suggested by the observation that the rodent hippocampus and entorhinal cortex are activated during the retrieval of recent but not of remote memories. One notable exception is the recall of remote memories for platform locations in the water maze, which requires an intact hippocampus and results in hippocampal activation irrespective of the age of the memory. These findings raise the question whether the hippocampus is always involved in the recall of spatial memories or, alternatively, whether it might be required for procedural computations in the water maze task, such as for calculating a path to a hidden platform. We performed spatial memory testing in radial maze tasks to distinguish between these possibilities. Radial maze tasks require a choice between spatial locations on a center platform and thus have a lesser requirement for navigation than the water maze. However, we used a behavioral design in the radial maze that retained other aspects of the standard water maze task, such as the use of multiple start locations and retention testing in a single trial. Using the immediate early gene *c-fos* as a marker for neuronal activation, we found that all hippocampal subregions were more activated during the recall of remote compared to recent spatial memories. In areas CA3 and CA1, activation during remote memory testing was higher than in rats that were merely reexposed to the testing environment after the same time interval. Conversely, Fos levels in the dentate gyrus were increased after retention testing to the extent that was also observed in the corresponding exposure control group. This pattern of hippocampal activation was also obtained in a second version of the task that only used a single start arm instead of multiple start arms. The CA3 and CA1 activation during remote memory recall is consistent with the interpretation that an older memory might require increased pattern completion and/or relearning after longer time intervals. Irrespective of whether the hippocampus is required for remote memory recall, the hippocampus might engage in computations that either support recall of remote memories or that update remote memories.

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### 1. Introduction

In human patients, damage to the medial temporal lobe or to the hippocampus alone causes retrograde amnesia – a loss of memory for information gained prior to the brain damage. In many cases, the pattern of retrograde amnesia is temporally graded, such that memories acquired close to the onset of the brain damage are lost while memories that were acquired a long time before the brain damage are not affected (Shrager, Bayley, Bontempi, Hopkins,

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& Squire, 2007; Squire, 1982). These findings suggest that the hippocampus has only a temporary role in memory storage and that long-term memories can be stored and retrieved by neocortical brain areas without a continued hippocampal contribution (Frankland & Bontempi, 2005; McClelland, McNaughton, & O'Reilly, 1995; Nadel & Hardt, 2011; Nadel & Moscovitch, 1997; Squire, Stark, & Clark, 2004; Winocur, Moscovitch, Rosenbaum, & Sekeres, 2010). Temporally graded retrograde amnesia is generally supported by data obtained from experimental animals with medial temporal lobe and hippocampal lesions (Kim, Clark, & Thompson, 1995; Kim & Fanselow, 1992; Lesburgueres et al., 2011; Maren, Aharonov, & Fanselow, 1997; Zola-Morgan & Squire, 1990). However, there are also studies that suggest a longer, if not continuous

involvement of the hippocampal formation in some types of memory, in particular if the retention testing requires pathfinding or the planning of routes (Broadbent, Squire, & Clark, 2006; Clark, Broadbent, & Squire, 2005a, 2005b; Kee, Teixeira, Wang, & Frankland, 2007; Martin, de Hoz, & Morris, 2005).

In addition to lesion studies, non-invasive functional brain imaging studies in behaving animals have importantly contributed to identifying how brain circuits reorganize during the transition from recent to remote memories (Bontempi, Laurent-Demir, Desfrade, & Jaffard, 1999; Maviel, Durkin, Menzaghi, & Bontempi, 2004). These studies used the visualization of immediate early genes (IEGs) to map neuronal circuits for remote memory formation. IEG expression is rapidly upregulated with neuronal activity that is associated with synaptic plasticity (Cole, Saffan, Baraban, & Worley, 1989), and these markers have generally shown that the hippocampus remains active during task acquisition as well as during retrieval testing within a period of several days. In contrast, if retrieval is tested after several weeks, the hippocampus and its adjacent cortical areas (e.g., subiculum, entorhinal cortex) are more weakly activated and prefrontal areas are more strongly activated (Maviel et al., 2004). While these findings were obtained using the radial maze, studies that used the Morris water maze found high levels of hippocampal activation during remote memory testing (Kee et al., 2007; Lopez et al., 2012).

Although testing in the water maze as well as in the radial maze requires memory for a specific spatial location, the experimental procedures necessarily differ in many other aspects, which might engage the hippocampus to different extents. The higher hippocampal activation on the water maze task, for example, could emerge from the higher demand for navigation (i.e., pathfinding or the planning of routes) in the water maze task compared to radial maze tasks. However, the testing procedures in previous studies that found lower levels of hippocampal engagement during remote memory testing also differed in other important aspects. For example, in a recent study by Lopez et al. (2012) memory testing in the water maze was performed during a single probe trial, while testing in the radial maze included multiple trials (Bontempi et al., 1999). Furthermore, testing in the water maze is usually performed using multiple start locations (Kee et al., 2007; Lopez et al., 2012), while testing in a radial maze task used a single start location (Maviel et al., 2004). With a single start location, the task might, after prolonged training, be solved with a striatum-dependent turning strategy rather than a hippocampus-dependent spatial strategy (Packard & McGaugh, 1996; Teather, Packard, Smith, Ellis-Behnke, & Bazan, 2005). This raises the possibility that a diminished hippocampal contribution at the end of the acquisition period might result in a lesser hippocampal engagement during remote memory testing. In addition, previous studies differed also in the construction of the retention test from the water maze. For example, Maviel et al. (2004) included a forced-choice presentation phase, which preceded the test phase by 20 min. Rather than remembering the location of the goal over several weeks, the task could thus also be solved by remembering the rule to return to the most recently presented arm over long intervals and by remembering the spatial location only over the short time interval between the sample and the choice phase.

To explicitly test whether the long-term retention of a goal location or whether procedural aspects of radial maze tasks result in diminished hippocampal activation, we performed a spatial memory task in the radial maze with multiple start locations and in which retention testing was limited to a single trial. This task has been shown to be hippocampus dependent throughout training (Cassel et al., 1998) and can, because of the single retention trial, only be solved by long-term memory for the goal location. The radial maze task thus shares these features with the standard version of the water maze but, in contrast to the water maze, has

low demand for spatial navigation because it merely requires that a choice is made on a central platform. To further reduce the navigational demand, we also used a radial maze task that required rats to learn a fixed trajectory. By visualizing the immediate-early gene product Fos as a marker for brain activation during a single retention trial, we could therefore distinguish whether the recall of spatial memories rather than high navigational demand might result in sustained hippocampal activation.

## 2. Material and methods

### 2.1. Animals and housing conditions

Male Long Evans rats ( $n = 46$ ) weighing 250–290 g at the beginning of the experiment were obtained from Taconic (Petersburg, USA) and group housed (4–5 rats per cage) in polycarbonate cages ( $60 \times 38 \times 20$  cm). The environmental temperature was  $22 \pm 2$  °C and the relative humidity  $55 \pm 10\%$ . The animals were submitted to a reversed light–dark cycle with artificial fluorescent lighting of 80 Lux from 8:00 p.m. to 8:00 a.m. and were tested during the dark phase of the cycle. Rats were food deprived to 85–90% of their free-feeding body weight and maintained at this level throughout the period of behavioral training and 1 week prior to the training and testing phases of the experiment. Water was available ad libitum. All experiments were carried out in accordance with the Norwegian Animal Welfare Act and the European Convention for the Protection of Vertebrate Animals used for Experimentation and Other Scientific Purposes.

### 2.2. Apparatus and testing environment

A 6-arm radial maze was placed in a  $2.4 \text{ m} \times 3.0 \text{ m}$  room. The maze consisted of a hexagonal central platform with a diameter of 30 cm from which 6 arms (85 cm long, 10 cm wide) radiated at equal angles. The maze was covered with black contact paper and was elevated 50 cm above the floor. A black food-well was placed at the end of each arm. A camera was mounted at the ceiling above the central platform and connected to a monitor and DVD recorder to track and record the rats' performance on the maze. During the intertrial intervals the animals were placed in opaque boxes ( $30 \times 40$  cm) in an area that was approximately 2 m from the maze and separated from the training area by 1.8 m high opaque dividers.

### 2.3. Behavioral tasks

Each rat was trained on one of two different reference memory tasks in the 6-arm radial maze (Fig. 1A). In each of the two tasks, rats were given five training trials per day with 20-min intertrial intervals. Sixteen rats were trained in a version of the task with a fixed goal location and five possible start positions that varied pseudorandomly from trial to trial (multiple start-arm task). Each start arm was used once during the five trials of each day. The use of multiple start locations in the radial maze renders the task hippocampus dependent (Cassel et al., 1998) and is a feature that is also used in the standard version of the water maze. Fourteen rats were trained on a version of the task with a fixed goal location and a single start arm (single start-arm task). Because both the start and the goal arm remained the same throughout training, the rats took the same trajectory during each correct trial. This task is similar to a task that has previously been used for imaging hippocampal activity patterns (Maviel et al., 2004), and it can be solved by using either a hippocampus-dependent place strategy or a striatal-dependent response strategy. However, an important difference between our version and the version that was used by

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