



## Validation and scopolamine-reversal of latent learning in the water maze utilizing a revised direct platform placement procedure



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### ABSTRACT

The Morris water maze is routinely used to explore neurobiological mechanisms of working memory. Humans can often acquire working memory relevant to performing a task by mere sensory observation, without having to actually perform the task followed by reinforcement. This can be modeled in the water maze through direct placement of a rat on the escape platform so that it can observe the location, and then assessing the subject's performance in swimming back to the platform. However, direct placement procedures have hardly been studied for two decades, reflecting a controversy about whether direct placement resulted in sufficiently rapid and direct swims back to the platform. In the present study, utilizing revised training methods, a more comprehensive measure of trajectory directness, a more rigorous sham-trained control procedure and an optimal placement-test interval, rats swam almost directly back to the platform in under 4 s, significantly more quickly and directly than sham-trained subjects.

Muscarinic cholinergic mechanisms, which are inactivated by scopolamine, are essential to memory for standard learning paradigms in the water maze. This experiment determined whether this would also be true for latent learning. ANOVA revealed significant negative effects of scopolamine on both speed and accuracy of trajectory, as well as significant positive effects of direct placement training vs. sham-training. In a probe trial, placement-trained animals without scopolamine spent significantly more time and path length in the target quadrant than trained rats with scopolamine and sham-trained rats without scopolamine. Scopolamine impairments are likely due to effects on memory, since the same dose had little effect on performance with a visible platform. The revised direct placement model offers a means of further comparing the neural mechanisms of latent learning with those of standard instrumental learning.

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### 1. Introduction

Latent learning has been defined as learning that is not apparent at the time of learning, but is manifested later when suitable motivation and circumstances appear. Such learning is initially acquired by observation or sensory experience without any performance or reinforcement of the specific behavior subsequently used to evaluate learning (Tolman and Honzic, 1930). A large proportion of human learning appears to meet this definition. Animal models of latent learning are necessary to answer certain questions. To what extent does latent learning depend on the same neurobiological mechanisms as ordinary instrumental learning (acquired by performing a behavior followed by reinforcement or punishment)? To what extent does learning through these procedures respond similarly to pharmacological interventions or to aging?

The water maze task (Morris, 1981) is a widely used test of learning and memory (D'Hooge and Deyn, 2001) that normally relies on negative reinforcement (i.e. escape from the aversive stimulus of deep water) to reinforce the behavior of swimming to a submerged platform. The possibility of latent learning in the water maze has not been extensively investigated for two decades, but previous research produced inconclusive and controversial findings. Sutherland and Lingard (1982) first investigated latent learning in the water maze by placing rats directly on the hidden platform, rather than letting the rat discover the location through random exploration. Directly placed rats swam back to the platform more quickly than control rats that were not placed on the platform prior to swimming trials. Keith and McVety (1988) were able to report similar findings. Their results indicated that rats can benefit from direct platform placement, but only if they had previously been trained to escape the water by swimming to a platform, even in a totally different environment. This was interpreted as indicating that a rat's knowledge of its spatial environment is stored independently of its history of behavior in that environment.

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However, Sutherland et al. (1987), Chew et al. (1989) and Whishaw (1991) challenged this interpretation, favoring an associative learning theory as opposed to cognitive learning. This argument rested heavily on observations that the directly placed rats, while returning to the platform faster than control subjects, did not exhibit “efficient” swimming behavior. That is, they did not swim back to the platform where they had been placed rapidly or directly enough to indicate “instantaneous transfer” from learning the platform location to swimming to that goal from another location on the edge of the pool.

Perhaps reflecting this controversy, there has been almost no published research for over two decades on latent learning by direct platform placement. The present research project attempted to modify the direct placement procedures to produce a more robust latent learning effect, as indicated by faster and more direct swims back to the platform location. Modifications included a more rigorous sham-training control procedure for comparison with the direct placement procedure. There was also a highly structured task familiarization procedure to more thoroughly teach the basic nature of the task (swimming back to the platform). Various placement-test intervals were evaluated.

Most importantly, a new metric utilized updated computer tracking software, to quantify the subject's accuracy relative to the direct route to the platform. This measure was based on the rat's entire trajectory to the platform from start to finish. This contrasts with the much more limited indicators of accuracy used previously: initial heading (Sutherland and Liggard, 1982), which pool quadrant was entered first (Keith and McVety, 1988) and whether or not the rat strayed at any point from an 18 cm corridor leading from the start position to the platform (Whishaw, 1991). As in some of the previous studies, a working memory version of the learning task was utilized. This allows repeated testing of the same animal with differing platform locations, reducing variability due to individual differences.

A second experiment attempted to reconfirm the basic findings of the first experiment. Additionally, by ascertaining the effects of muscarinic cholinergic blockade, it took a first step toward comparing the underlying neural mechanisms of latent learning in the water maze with those of standard instrumental learning. Pharmacological studies have revealed a link between muscarinic cholinergic receptors and cognition by showing that drugs known to inhibit these receptors impair cognitive processes in humans and animals, while drugs that stimulate acetylcholine transmission can enhance cognition (Tsui and Dringenberg, 2013). Scopolamine is a muscarinic receptor antagonist that blocks activation of all subtypes of muscarinic acetylcholine receptors (Yamada et al., 2004). Scopolamine has been shown to impair working memory in human subjects (Ellis et al., 2006; Lenz et al., 2012; Thomas et al., 2008; Wesnes et al., 1998). A number of studies have shown that scopolamine also impairs working memory acquired through standard instrumental learning procedures in the water maze (Bertrand et al., 2001; Buresová et al., 1986; Doguc et al., 2012; Kikusui et al., 1999; Lindner et al., 2006; Pitkänen et al., 1995; Santucci et al., 1995; Von Linstow Roloff et al., 2007). Experiment 2 determined whether latent learning in the water maze was likewise dependent on muscarinic cholinergic mechanisms. To our knowledge, there are currently no published studies of scopolamine's effect on any form of latent learning in rodents. Experiment 3 evaluated whether the scopolamine impairment might be due to interference with sensory-motor or motivational functions as opposed to memory effects. It tested the effects of scopolamine on speed and directness of swimming to a visible platform.

## 2. Methods

### 2.1. Subjects

The subjects were 54 male Long-Evans hooded rats (Harlan, Indianapolis, IN). They ranged from 9–13 months of age in Experiment 1 and from 6 to 8 months of age in Experiments 2 and 3. They were

housed two per cage in a controlled environment with a 12 hour light–dark cycle and food and water available ad libitum. They were handled for three days prior to the experiment. All procedures were approved by the university's Institutional Animal Care and Use Committee and conform to the *Guide for the Care and Use of Laboratory Animals*, 8th ed. (2011).

### 2.2. Apparatus

A test pool, 140 cm in diameter and 59 cm in depth, was used for all retention testing and for relevant training. It contained water made opaque by nontoxic, water-soluble paint. A 20 × 20 cm platform was submerged approximately 2 cm below the surface. The pool was in a 3 × 4.5 m room and was surrounded by several distinctive spatial cues, including a white curtain, laboratory furniture, and large black shapes affixed to the wall. Swimming performance was recorded with a computerized video tracking system (Videomex, Columbus Instruments, Columbus, OH).

For “sham training”, a 60 cm diameter barrel with a centered platform submerged under opaque water was used to control for the experience of being placed on a submerged platform. This “sham training” apparatus was located in a different, nearly empty room without any visual cues relevant to the actual test apparatus.

### 2.3. Task-familiarization procedure

All rats were trained in the actual test pool on three consecutive days to return to the location of a submerged escape platform where they had been placed. The location of the escape platform changed every day. On each day of task familiarization, subjects were placed on the platform in the pool for 45 s in Experiment 1 and 30 s in Experiment 2 and allowed to observe their surrounding environment, cues and landmarks. The reduced placement time in Experiment 2 was intended to add a slight amount of difficulty to the task. Following platform placement on Day 1, the subjects were taken out of the water, towel-dried, placed on a heating pad and allowed to rest for 60 s. They were then placed 15 cm away from the platform, required to swim back to it, and allowed to remain on the platform for the designated time. If they were not able to find the platform within 60 s, they were guided to the platform and placed there for the usual duration. This procedure was repeated three times with rats placed at 30 cm away from the platform, then 45 cm, then at the edge of the pool, each time in a different direction from the platform. The interval between each platform placement and each return swim was one minute on the first day of task familiarization, three minutes on the second day and five minutes on the third day. On all these familiarization trials, the locations of platform and starting points for the return swim were counterbalanced between subjects.

### 2.4. Experiment 1 procedure: working memory for latent learning

After three days of task familiarization, testing began on Day 4 and continued for six days. Each subject was given only one trial per day, and the platform was moved to a new position each day. (The nine possible platform positions were adapted from Steele and Morris, 1999.). Rats were randomly assigned to either a trained or sham-trained control group ( $n = 12$  per group). Each day, the subjects in the experimental group were directly placed for 45 s on the target platform in the water maze. The sham-trained control subjects were placed on a platform in the water-filled barrel in a different room. All subjects were then tested in the actual water maze and given a swim trial from a starting position on the edge of the pool. Starting positions for each rat varied over the six days and were counterbalanced among the subjects. There were intervals of 5, 10 and 30 min between direct placement and the swim trial, each interval occurring twice during the six days. The order of these intervals was also counterbalanced among subjects. On every trial, each

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