



Variants of the Morris water maze task to comparatively assess human and rodent place navigation



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ABSTRACT

Performance in the Morris water maze has been widely used in routine behavioural studies of rodents. Since the advent of computer-based virtual environments, adaptations of the water maze have become available for human research. Despite decades of comparative neuroscience, formal comparisons of human and animal place navigation performance are rare.

We studied 36 subjects, 18 young male mice in a Morris water maze and 18 male students in a virtual version. Quantitative measures (escape latencies, distances and platform crossings) indicated no discernable differences between human and rodent performance, reinforcing the task's general validity and its implied cross-species comparability. However, we extracted, using an a priori free classification method, qualitatively different movement patterns for mice and humans, patterns that reflect the probable strategy that individuals might have been using to solve the task.

Our results indicated young male students to have most likely solved the maze by means of spatial strategies whereas mice were observed more often to have adopted non-spatial strategies. These differences could be attributed to differences in our maze setups (spatial cues, task instruction, training protocol, motivation) and gave further hints that maze learning depends on many factors. In summary performance on both spatial tasks was equivalent in humans and mice but the kind of maze learning that was used to achieve maximum performance was different.

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1. Introduction

Morris (Morris, 1981) first introduced the water maze apparatus, which involved testing rodents in a large pool of milky water, requiring them to swim to a fixed submerged platform in order to escape from the water. Only distal room cues defined the location of the platform, so that to do this, animals had to use 'place navigation'. This term describes behaviour in animals indicated by a directed movement (navigation) toward a single spatial location (place) (Morris, 1981). Place navigation occurs under conditions of trial-by-trial learning and recruits brain regions that are crucial in spatial memory formation. Many studies have indicated that hippocampus-dependent encoding, consolidation, and retrieval

are essential for spatial memory in rodents (Brandeis, Brandys, & Yehuda, 1989; D'Hooge & De Deyn, 2001; Nakazawa et al., 2003; Nunn et al., 1994). The Morris water maze apparatus is inseparably associated with these kinds of study. It has become one of the most important behavioural tasks for the assessment of spatial learning and place navigation, and a wide variety of apparatus configurations and testing procedures have been employed during recent decades of animal research. The most common configurations and procedures were catalogued by Vorhees and Williams and described in a standardized fashion in Nature Protocols (Vorhees & Williams, 2006).

With the advent of modern 3-D computer technology, adaptations of Morris' water maze task have become available for assessing human spatial behaviour and spatial memory. Usually, inferences from rodent to human behaviour have been made with great confidence (Bartsch et al., 2010; Goodrich-Hunsaker, Livingstone, Skelton, & Hopkins, 2010; Rodriguez, 2010; Schoenfeld, Foreman, & Leplow, 2014). However, the examination of spatial memory in animals – predominantly rats for the Morris

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water maze task – and examination of spatial memory in humans have arisen from research with very different backgrounds and methodologies. The water maze task became popular for use with animals in part because it was easy to conduct; it was not necessary to have animals food- or water-deprived, since with neither deprivation they were still highly motivated to perform. An animal learns across successive trials to move progressively more efficiently and directly to the platform in order to escape an aversive situation (i.e., swimming in the water). It should be mentioned that the Morris water maze has some limitations for use with mice. Rats seem to be more appropriate for water maze testing, because they are better swimmers, tend more often toward using spatial than response strategies, and they are more appropriate for electrophysiological studies. Moreover, researchers can administer them more trials with shorter inter-trial durations before they become exhausted. Exhaustive reviews of protocols available for rats have been provided by [Hodges \(1996\)](#) and by [Bolding and Rudy \(2006\)](#). The advantages of using mice in water maze testing are smaller pool size and lower housing costs.

The water maze procedure thus incorporates two main types of learning: instrumental conditioning (via negative reinforcement), and also place learning, since the platform must be spatially located via motoric spatial displacements in order for the instrumental response to be completed successfully. In contrast, virtually all computerized human water maze variants provide neither an aversive situation nor real locomotion, and hence may recruit different aspects of learning and memory. However, humans seem to be able to acquire spatial information from virtual mazes, which later on is available in comparable real environments ([Foreman, Stirk, Pohl, et al., 2000](#)).

Studies of brain structures in the mammalian medial temporal lobe, especially the hippocampal formation, have demonstrated their significant role in spatial memory formation as well as spatial behaviour generally. For example, in the first study to introduce the Morris water maze ([Morris, Garrud, Rawlins, & O'Keefe, 1982](#)), a lesion study with rats showed profound place navigation impairment after hippocampal damage, since after such damage animals swam about the pool randomly and haphazardly, only escaping when they happened to bump into the platform by chance. Similarly in humans, hippocampal micro insults, which are the core brain pathology in a transient global amnesia, resulted ostensibly in the same severe place learning deficit, measured by means of a virtual water maze ([Bartsch et al., 2010](#)).

The kinds of cognitive ability and learning mechanisms utilised by rodents while navigating the Morris water maze is under controversial debate; this has been reviewed in more detail elsewhere ([Sutherland & Hamilton, 2004](#)). It has been proposed that with regard to the reference memory task, rodents must use place learning. In the context of the Cognitive Map Theory ([O'Keefe & Nadel, 1978](#)) this type of learning is hippocampus-dependent and associated with the formation of hippocampal place cell fields. The theory describes the function of these cells in forming associations between distinct places in space and an array of more than one environmental distal cue (landmark). This hippocampal function is the basis of allocentric orientation, where the reference frame is centred in relation to the surrounding environment. In contrast, egocentric orientation has a body-centred reference frame and is based on sequences of simple movement instructions and proximal cues, such as “turn left at the next corner”. The Morris water maze apparatus was obviously designed to test for allocentric orientation skills, though doubts have been raised because some studies showed that animals with hippocampal damage could solve the reference memory task under some circumstances ([Ramos, 2010](#)), or that overtrained individuals could perform by switching from allocentric to egocentric orientation during the task ([Iaria, Petrides, Dagher, Pike, & Bohbot, 2003](#); [Kallai et al., 2007](#)).

In recent work [Konishi and Bohbot \(2013\)](#) showed, with the aid of a virtual navigation task, that volume of hippocampal gray matter is related to spontaneous strategy use. Older adults with larger hippocampal gray matter volumes tended more often to use spatial strategies than egocentric response strategies. Interestingly, task performance per se did not correlate with gray matter volume, indicating that people with distinct brain damage might nevertheless be able to reach a comparable quantitative performance level. In this context, a distinct role for the right hippocampal formation has been indicated in the performance of spatial navigation. [Bohbot et al.](#) used a battery of spatial tests for humans, adapted from a set of established animal tasks, to evaluate this issue ([Bohbot et al., 2002](#)). In an fMRI study the association between spatial strategy use and the activation of the right hippocampus has been further demonstrated ([Bohbot, Iaria, & Petrides, 2004](#)). Egocentric response strategies were instead associated with activation of the Nucleus Caudatus.

Although analogues of the Morris water maze have become widely used to test spatial learning and memory and its underlying brain structures in humans ([Bartsch et al., 2010](#); [Goodrich-Hunsaker et al., 2010](#); [Rodriguez, 2010](#)), only a few studies have considered the more technical aspects of the task beyond the place learning paradigm associated with water maze testing. A series of experimental variations of the apparatus and its surrounding features have raised additional doubts about the paradigmatic hippocampus-associated place memory dependency of the Morris water task ([Hamilton, Akers, Weisend, & Sutherland, 2007](#); [Hamilton et al., 2008](#)). Virtually all variants of the maze induced directional rather than place responses. This became more evident as the number of training trials increased, indicating a switch from cognitive place-dependent behaviour to a simpler motor response. Performing the same experiments in a virtual analogue of the water maze led to the same preference for directional responses, suggesting an equivalent shift in humans ([Hamilton, Johnson, Redhead, & Verney, 2009](#)). These studies allowed the determination of how extra- and intra-maze cues influenced water maze performance and the response strategies adopted to perform the task.

However, no cross-species study so far has considered the possible differences in maze performance driven by learning protocols that give several days of training compared to those that train the individuals in only one day. The latter is the standard approach in virtually all human maze studies. However, there is now clear evidence that stable memory formation can depend upon processes occurring during sleep, over-night consolidation seeming to be a sleep-stage dependent replay mechanism ([Diekelmann & Born, 2010](#); [Ji & Wilson, 2007](#); [Walker & Stickgold, 2004](#); [Skaggs & McNaughton, 1996](#); [Bendor & Wilson, 2012](#)). Indeed, during shorter inter trial delays hippocampal CA1 cells seem to display enhanced firing, and the patterns of that firing are different from the patterns seen in replay firing during sleep-stages. The purpose of replay firing is so far unknown, but it is assumed to replay the most recent experiences, in that case the most recently walked paths in space ([Gill, Mizumori, & Smith, 2010](#)). For that reason it is clear that water maze learning might be different, depending on whether the training procedure incorporates longer over-night, or short inter-trial, periods.

We hypothesized that maze learning and memory performance will depend upon the learning protocols that are employed. The technical aim of this study was to develop and evaluate a computer-based (virtual) water maze as an analogous test of spatial learning and memory in humans, and test the circumstances under which the virtual maze is comparable to the Morris water maze task, using comparable behavioural measures, and both within-day and across-days learning protocols.

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