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Spatial Learning and Memory—What's TLE Got To Do With It?

Geoffrey G. Murphy^{1,2}¹Molecular and Behavioral Neuroscience Institute, University of Michigan Medical School, Ann Arbor, MI²Department of Molecular and Integrative Physiology, University of Michigan Medical School, Ann Arbor, MI

Address correspondence to Geoffrey G. Murphy, University of Michigan, 5037 Biomedical Science Research Building, 109 Zina Pitcher Place, Ann Arbor, MI 48109-2200; E-mail: murphyg@umich.edu

Cognitive impairment is a significant comorbidity of epilepsy. At present, the molecular/cellular mechanisms that underlie these cognitive impairments remain unknown. It seems likely that a complete understanding at the molecular/cellular level will require the use of rodent models. A number of rodent models of epilepsy are used to study cognition in a variety of behavioral tasks. This review presents a brief overview of two commonly used tasks (the Morris water maze and the radial arm maze) that have been used to assess spatial learning/memory in two chemoconvulsant models of temporal lobe epilepsy.

Although not all forms of epilepsy occur concomitant with cognitive impairments, a wide range of epilepsy syndromes appear to be associated with altered cognition, including deficits in memory consolidation and retrieval (1). It has long been appreciated that the hippocampus plays a critical role in the acquisition and consolidation of long-term declarative memories (2). Therefore, it is not altogether surprising that syndromes such as temporal lobe epilepsy (TLE), which preferentially impact temporal lobe structures including the hippocampus, have been linked to seizure-related cognitive impairments. Of the various epilepsies that have been linked to seizure-related memory impairments, the impact of TLE on cognition has been most intensively studied. This focus has been mainly driven by pre-/postsurgical cognitive evaluations of patients with chronic, drug-resistant TLE who have undergone surgical resections of the temporal lobe (3). Substantial refinements of neuropsychological metrics used to examine TLE patients have been made, leading to a number of hypotheses regarding the neuropathology that might underlie TLE-associated cognitive deficits (4). However, it seems likely that a complete understanding of the relationship between TLE and seizure-related cognitive impairments will require, at least in part, a detailed investigation at the cellular and molecular level, which at present is not possible with human subjects. Therefore, a number of groups have examined cognitive function in various rodent models of TLE (rTLE models). The review that follows is intended to give a brief overview of two popular behavioral tasks used to investigate spatial learning/memory, highlighting their respective advantages and disadvantages for studying learning/memory in rTLE models. Space constraints limit a more exhaustive review.

Spatial Learning/Memory and the Hippocampus

In the broadest sense, memory can be subclassified into forms that are either declarative or nondeclarative. Declarative memories are memories of facts or events that require conscious recall, whereas nondeclarative memories are typified by simple classical conditioning or skill/habit learning that can be acquired non-consciously (5). The formation or encoding of declarative memories is known to require structures in the temporal lobe, including the hippocampus (2). In humans, much of what we know regarding the obligatory role that temporal lobe structures play in the formation of declarative memories comes from descriptions of patients with hippocampal lesions. Perhaps the most well studied of these is patient H.M. (Henry Molaison 1926–2008), who exhibited profound and persistent anterograde amnesia following a bilateral temporal lobe resection, which included hippocampal ablation (6). Since this earlier report, other patients have been identified with much more restricted hippocampal lesions in which the surrounding temporal lobe structures are spared. Although the deficits in declarative memory in these patients are less severe than those observed in patient H.M., data from these patients is consistent with the assertion that the hippocampus plays a key role in the formation of long-term declarative memories (2).

In rodents, bilateral damage of the hippocampus leads to impairments that, in many respects, resemble the anterograde amnesia observed in the human patients mentioned above. Of the multiple forms of “declarative-like” memories that are disrupted following hippocampal damage, the disruption of spatial learning and memory has been studied most intensively. While several theories have been advanced (7–9), the exact mechanism(s) for how the hippocampus (and associated cortices) encodes spatial information remains to be elucidated. However, there is general agreement that molecular/cellular and neuroanatomic manipulations that disrupt normal hippocampal function typically disrupt the effective encoding of spatial information.

Using the Morris Water Maze to Assess Spatial Learning/Memory

A key first step in understanding the neurobiological basis of the memory impairments associated with TLE would be the demonstration that learning and memory in established rTLE models is in fact disrupted. Beyond this, it seems likely that once established, these models would be valuable in developing and testing putative therapies to ameliorate these cognitive impairments. Given the known relationship between hippocampal function and spatial learning/memory, there has been a considerable effort to investigate the impact of experimentally induced TLE on spatial learning/memory. A literature survey indicates that the most popular method for assessing spatial learning/memory in rTLE models to date has been the Morris water maze (MWM). Since the original description (10), the MWM has been repeatedly used to demonstrate that disruptions in hippocampal function disrupt spatial learning/memory (11). The MWM has a number of desirable qualities in terms of assessing spatial learning/memory. The physical setup is fairly simple, and there are a number of commercially available software packages for MWM acquisition and analysis that are relatively inexpensive. In addition, quite a large number of animals can be run each day, allowing for multiple group comparisons.

The typical apparatus consists of a large circular pool filled with water that has been made opaque with a nontoxic paint. Animals are released from random start locations around the perimeter of the pool and allowed to swim to an escape platform hidden just below the surface of the water. Because the platform is not visible, animals must use the distal cues in the room to navigate the platform location. Animals are typically given multiple trials within a day, and multiple days of training. Early in the training, many animals will fail to find the hidden platform within the time allotted for the trial (typically 1–2 minutes), in which case they are nudged toward the platform or, in some cases, placed directly on the platform. During this phase of the task (often referred to as the acquisition or training phase), the animals' performance is assessed by the amount of time required to locate the platform (termed escape latency) or, alternatively, the distance traveled before reaching the platform. It has long been recognized that these measures are not sufficient to assess whether or not an animal is using the distal cues to locate the hidden platform. Animals that are truly impaired in spatial learning can often achieve relatively short escape latencies by adopting a circular swim pattern at a fixed distance from the edge of the tank. Therefore, an independent measure is often required to differentiate adaptive strategy and true spatial learning/memory. This is easily accomplished by periodically making the platform unavailable or removing the platform all together. During these trials—aptly named probe trials—the pool is divided into four imaginary quadrants, and the amount of time (or the distance traveled) in the four quadrants is assessed. A successful search strategy is indicated if the animal spends significantly more time in the quadrant in which the platform was previously located. Typically, animals that have adopted a nonspatial search strategy will spend, on average, equal amounts of time (or distance) in each of the four quadrants. Although probe trial performance is often assessed at the end of multiple days

of training, probe trials can be (and perhaps often should be) administered multiple times across the training period.

One significant drawback of using the MWM is that performance during training as well as in probe trials can be significantly affected by a number of noncognitive related factors. To control for alterations in motivation, visual acuity, and motor/procedural performance, the same animals should be tested using the nonspatial hippocampal-independent version of the MWM. This version of the task (often referred to as the cued version) is identical to the hidden-platform version except that, in this version, the platform is clearly marked and is moved from trial to trial. Cued training can be completed before the start of the hidden-platform training to eliminate animals that might not be suitable for the hidden-platform training (e.g., owing to motor deficits). Additionally, motor performance during the training and probe trials can be quantified by swim speed. Although alterations in swim speed can be a potential confound during the training trials and the probe trials, deficits in swim speed can be negated by using Gallagher's proximity measure (12). The proximity measure, which was developed for use with aged rodents, is calculated by measuring the animals' proximity to the platform during the trial typically at 0.1-second intervals. The swim speed of each animal is calculated, and the amount of time that would have been required to swim directly from the start location to the platform is subtracted from the record prior to calculating the proximity measure. As such, the calculated proximity measures represent the animals' deviation from the ideal search pattern and are independent of swim speed. During training trials, the proximity measurements are summed to generate a cumulative proximity score, whereas during the probe trial, these values are averaged. Most commercially available tracking software now includes the Gallagher proximity measure.

Spatial learning/memory in the MWM has been evaluated in the kainic acid (KA) and pilocarpine models of TLE in rats (13–15) as well as mice (16, 17). Generally speaking, the results from these studies are consistent in that they all report disrupted performance in the MWM as measured by latency to reach the platform during training or time/distance in each training quadrant during probe trials. Although the visual platform version of the task was not used in every study, at least two of these studies (14, 15) found deficits in the latency to reach the visible platform. The Inostroza et al. study (14) is particularly noteworthy in that this study was designed to directly compare spatial learning in the two different rTLE models (KA and pilocarpine) in two different rat strains (Wistar and Sprague-Dawley). When examined in the cued version of the MWM, rats treated with pilocarpine, regardless of strain, were unable to find the visible platform. Not too unexpectedly, these animals were also unable to learn in the hidden platform version of the MWM. It is not clear exactly why the pilocarpine-treated rats performed so poorly in the cued version of the MWM, but it certainly reinforces the importance of this control. It is also worth noting that in both models (and in both strains), rats exhibited significant thigmotaxis (wall hugging), a behavior that is often associated with alterations in affective state. In this report (14) and in a subsequent study (18), the authors demonstrate a complex relationship between chronic seizure activity and affective behaviors. It appears that many



factors contribute to this behavior (e.g., severity of seizures, extent of brain damage, strain differences), but again, this example is presented to emphasize the need for critical evaluation of the “standard” measurements assessed in the MWM.

Using the Radial Arm Maze to Assess Spatial Learning/Memory

Although not as widely used as the MWM, the radial arm maze (RAM) has been used to investigate spatial learning/memory in some rTLE models. The most common form of the RAM is the eight-arm version first introduced by David Olton in the mid 1970s (19). As the name implies, the radial arm maze is constructed of a central hub with eight arms that radiate out from the center. Typically, each arm contains a reward cup that can be filled with small food pellets or treats. Therefore, the primary motivation in this task is food reward (or sometimes water), which is meant to exploit the animals’ natural foraging behavior. The RAM can be configured and run in a number of different ways. The typical and most common version of the RAM is where all arms are baited, and the rodent is released from the center hub and allowed to freely forage until all reward cups have been visited. This form is typically used to examine spatial working memory, with the idea that rats or mice will not return to forage at a site where they have previously consumed all of the food. Therefore, a return trip to a previously visited arm is considered a working-memory error. Alternatively, a subset of arms can be consistently baited during training. In this version of the RAM, working memory errors are assessed as previously described, but entries into an arm not consistently baited are reflective of long-term spatial learning/memory impairments. Both forms of the task have been previously demonstrated to be sensitive to disruptions in hippocampal function (20, 21). The RAM has the advantage of being somewhat less demanding in terms of motor output than the MWM, and performance is based more on the animal’s choice to enter a baited or non-baited arm. Therefore, the performance is somewhat easier to assess, and in most cases would not necessitate the use of tracking software. One potential disadvantage of the RAM is that in most cases the animals must be food deprived to sufficiently motivate them to forage on the maze.

There have been a number of reports examining rTLE models using the RAM to examine spatial working memory. For example, rats (Sprague-Dawley) exhibiting spontaneous seizures for 5 months following pilocarpine induction of status epilepticus exhibited significant impairments in spatial working memory assessed by baiting all eight arms and scoring reentry errors (22). Similar results have been obtained using the KA model (23). However, these authors did not find spatial working-memory deficits using the RAM when rats were kindled from the amygdala, suggesting that the deficits in spatial learning/memory were due to the severity of lesions or structural reorganization in the hippocampus and not seizure activity alone (23).

Several reports describe deficits in reference memory using the RAM. The reference memory task version of the RAM seems particularly sensitive to impairments in spatial learning/memory when status epilepticus is induced early in development. Kainate acid injections given at postnatal day 1, 7, 14, or

24 produced significant deficits in spatial reference memory when assessed in young adulthood (24). Similarly, when pilocarpine was used to induce status epilepticus, rats that experienced prolonged seizures were more likely to enter a non-baited arm during testing. Compared with control rats, the rats that received the pilocarpine injections showed significant cell loss in the CA1 region of the hippocampus (25). In addition to being sensitive to spatial learning/memory deficits in the chemoconvulsant models of TLE, reference memory assessed by the RAM is significantly impaired in rats that received hippocampal (26) or olfactory bulb (27) kindling.

Another advantage of the RAM is that it can be configured and run in a variety of ways. The task can be made simpler or more difficult without changing the physical demands of the task or by adding additional dependent variables. For example, in the reference-memory task, fewer arms could be used (e.g., consistently baiting only two arms). Conversely, the RAM can be run such that the cognitive demands are much greater. Perhaps the best example of this flexibility comes from early work by Packard and colleagues who developed a delay win-shift paradigm for the RAM (28). In the delay win-shift paradigm, training consists of one session per day, with each session being composed of two phases. During the first phase (trial A), four of eight arms are baited. The animal is placed in the center hub, and the doors to these four arms are opened, while the remaining four doors are kept closed. The animal is allowed to enter the arms and retrieve the reward pellets until all the pellets are consumed, at which time the animal is removed from the maze and placed in a holding cage for some delay, during which time the maze is cleaned. In the second phase (trial B), the alternate four arms are baited. The animal is returned to the center of the maze and all eight doors are opened. Thus, the delay win-shift version of the task forces the animals to forage prospectively using information acquired before the delay to predict the correct arms on the subsequent trial (29–31). In this version, the difficulty of the task can be manipulated by varying the delay between the two phases. Therefore, in addition to being more cognitively demanding, the delay win-shift version of the RAM has a control for motivation and motor performance built into the task such that delay-dependent impairments reflect the impact of increased cognitive load and not deficits in noncognitive domains. Previously, we have used the delay win-shift version of the RAM to study cognitive impairments in aged mice (32). In these experiments, we were able to demonstrate that at short delays, aged mice performed at similar levels when compared with control mice. However, when the delay between phases was expanded, aged mice were significantly impaired, making more entries into arms that were previously visited on the first phase. This version of the RAM might be well suited to study spatial learning/memory in rTLE models, when alterations in sensory/motor function or affective behavior are suspected.

Conclusions

Cognitive impairments that can accompany epilepsy, especially TLE, represent a significant disease comorbidity. In humans, these impairments are quite heterogeneous and dependent upon many factors. A key step in better understanding the relationship between TLE and cognitive capacity will undoubtedly



edly require a basic understanding of the molecular/cellular changes that underlie the cognitive impairments. Therefore, the development of reliable and robust behavioral models represents a key first step. Evidence using the Morris water maze and the eight-arm radial maze suggests that multiple forms of spatial learning/memory are disrupted following the induction of status epilepticus in both mice and rats. Given the significant motor output required for these tasks (especially the water maze), care needs to be taken to control for confounding, noncognitive performance deficits in these tasks. The ultimate goal of this research is to better understand learning/memory impairments in humans with epilepsy. To this end, it will be important to examine a wide range of behavioral tasks that have been exploited to study learning/memory in other contexts, and to evaluate these paradigms using a broad and diverse set of rodent epilepsy models.

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