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Research report

Assessing rodent hippocampal involvement in the novel object recognition task. A review

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HIGHLIGHTS

- Recent papers on the role of hippocampus in NOR are reviewed.
- Object recognition is a well accepted task for testing rodent nonspatial memory.
- Temporary and permanent hippocampal lesions inconsistently affect NOR performance.
- Differences in exploration criterion and delay confound interpretation of results.
- Need for the standardization of NOR procedures is stressed.

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ABSTRACT

The novel object recognition (NOR) task has emerged as a popular method for testing the neurobiology of nonspatial memory in rodents. This task exploits the natural tendency of rodents to explore novel items and depending on the amount of time that rodents spend exploring the presented objects, inferences about memory can be established. Despite its wide use, the underlying neural circuitry and mechanisms supporting NOR have not been clearly defined. In particular, considerable debate has focused on whether the hippocampus plays a significant role in the *object* memory that is encoded, consolidated and then retrieved during discrete stages of the NOR task. Here we analyzed the results of all published reports in which the role of the rodent hippocampus in object memory was inferred from performance in the task with restricted parameters. We note that the remarkable variability in NOR methods across studies complicates the ability to draw meaningful conclusions from the work. Focusing on 12 reports in which a minimum criterion of sample session object exploration was imposed, we find that temporary or permanent lesion of the hippocampus consistently disrupts *object* memory when a delay of 10 min or greater is imposed between the sample and test sessions. We discuss the significance of a delay-dependent role of the hippocampus in NOR within the framework of the medial temporal lobe. We assert that standardization of the NOR protocol is essential for obtaining reliable data that can then be compared across studies to build consensus as to the specific contribution of the rodent hippocampus to object memory.

1. Introduction

We can all recall a time when walking down a crowded corridor, we happen upon a person who looks familiar. While we are confident that we have encountered this person before, we are unable to remember how or when we previously met. It is only through the information gathered during interactive conversation that we are able to recall who this person is and where we encountered them for the first time. This uncomfortable, yet common, scenario depicts our ability to subjectively recall previous information through distinct memory processes.

Memory can be divided into two distinct categories, declarative and non-declarative forms. Declarative memory, or explicit memory, is the ability to recall personal history, facts and events, and is dependent on the interconnected structures of the medial temporal lobe. Recognition, a subtype of declarative memory, reflects

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that of people, objects, and experiences. Clearly, the example stated above illustrates the two forms of recognition memory that are commonly experienced during a test of information retrieval, that is, familiarity and recollection. Familiarity is the immediate feeling that an event, individual, or item was previously encountered. This experience, referred to as 'knowing', does not involve the conscious recollection of details from the prior experience. For example, *"I know I have seen that person (or item) before; I just don't remember where or when"*. Recollection, or 'remembering' on the other hand, involves a slower process whereby full attention to the present stimuli (if any) induces an intended or conscious recall of the contextual details of the prior event or experience – that is, specific information as to where and when the original experience occurred [1,2]. For example, *"I remember you. We met at the 2012 Society for Neuroscience meeting; our posters were next to one another on the second day of that conference, and you commented on how well I coordinated my outfit with the color scheme of my poster"*. Originally defined by Tulving [3], the remember/know distinction is considered by many to reflect separate underlying behavioral processes of recognition memory. Although the processes of recollection and familiarity are distinct in the manner that they are experienced, it remains unclear whether different neurobiological mechanisms support them. Dual-process models of recognition memory state that recollection and familiarity are functionally separate systems [4–8]. Studies of human amnesiacs have revealed selective impairment of recollection, while sparing familiarity, and numerous functional imaging studies have identified that the separate processes are associated with region-specific activation patterns. These findings are largely considered support for the view that familiarity and recollection utilize different underlying systems [9–11]. On the other hand, single-process models view the two declarative memory forms as a part of one distinct category of recognition memory [7,10,12]. Here, memories are represented along a scale that ranges from weak to strong. Studies have demonstrated that these two processes have a significant structural commonality that would point to a single process model. Similar structural activation is observed with both familiarity and recollection [11]. Regardless of how these forms of memory are thought to function, the fundamental concepts derived from the distinction between familiarity and recollection are useful for improving understanding of recognition memory mechanisms in both humans and laboratory animals.

The medial temporal lobe is organized in a manner that supports memory. Various sub-regions have been identified as the structures critical in supporting memory in a variety of species [13]. The perirhinal cortex, parahippocampal cortex, and entorhinal cortex are anatomical structures identified as components of the "*what*" and "*where*" streams of experience-dependent sensory inputs that converge within the hippocampus. Traditionally, it is believed that the "*what*" information is conveyed through the perirhinal cortex, while the "*where*" information is transmitted through the parahippocampal and entorhinal cortices. It is only in the hippocampus that the "*what*" and "*where*" information is associated [1]. However, in recent years, debate over whether the hippocampus is directly involved in encoding memories of the "*what*" information has increased. Similarly, many studies claim that familiarity is structurally distinct from that of recollection, with familiarity attributed to the perirhinal cortex and recollection to the hippocampus [14]. Nevertheless, it is apparent that during recollection, it is the "*what*" and "*where*" associations that are being recovered.

In general, memories are formed and stabilized through three distinct processes. Encoding refers to the initial acquisition of the memory. Then, through phases of consolidation, the memory is preserved and stored for later recall. Finally, retrieval is the process by which the previously stored memories are reactivated. Many different tasks have been developed to investigate the neural basis of memory and its distinct stages. However, it is important to note that all methodologies have limitations, which should be considered when analyzing outcomes. Human recognition memory is commonly tested in the visual paired comparisons task [15, see review 16], while a modified version of the task has been implemented for rodents [17]. Functional imaging studies, in humans, have identified patterns of region-specific neural activation associated with recollection and familiarity; however, animal models enable investigation of the neurobiological circuitry and cellular mechanisms of recognition memory, which are not possible in humans.

2. Novel object recognition

2.1. Task procedures and behavior quantification

Implicit to the animal model approach is the necessity that the behavioral constructs that are modeled in rodents match to a large extent, human recognition memory. To this end, the spontaneous novel object recognition (NOR) task has emerged as the most popular test for assessing a rodent's ability to recognize a previously presented stimulus [18]. Describing the task as such is misleading since it is not theoretically possible to *recognize* a novel object since recognition reflects prior exposure. While some have begun to adopt the more accurate phrase, *spontaneous object recognition* (*SOR*), most investigators continue to use *novel object recognition* or NOR in referring to the task. For the purposes of this review, we will refer to the aforementioned task as NOR; however, we assert that this designation does not adequately describe the object recognition memory that it can be inferred from it. Regardless, the NOR task has become the hallmark method used in assessing non-spatial object memory in rodents. Although there is considerable variability across labs in the NOR procedures used, most conduct the test in a familiar square or rectangular high-walled arena lacking polarizing spatial cues (see schematic in Fig. 1 for a depiction of the most commonly applied variation of the NOR task). In an effort to further reduce contextual and spatial information, a Y-maze arena has been used in several influential studies [19–22]. Although this novel design reduces contextual information, reports using square or rectangular arenas limit spatial cues by minimizing all visual, textural, and odor stimuli. During what is referred to as the training or *sample session*, the rodent explores two identical novel objects encountered in a familiar arena. Object memory encoding is operationally defined as occurring during the sample session. Upon completion of the sample session the animal is removed from the arena for some specified amount of time (i.e., retention delay), during which the object memory is consolidated. For the subsequent *test session*, the rodent is returned to the same arena, which now contains an exact replica of the familiar object and a novel object, as a test of object memory retrieval. Rodents are self-motivated to spontaneously approach items and explore using multiple senses. Object exploration behavior is easily quantifiable and allows for the study of episodic-like memories in rodents. Rodents exhibit a natural proclivity to explore novel, non-threatening objects, and therefore, during the test session rodents exhibit a preference for exploring the novel object significantly more than the familiar one. Thus, sample object memory strength is inferred from the preference of the rodent to explore the novel object over the familiar object during the test session. Object memory is quantified by computing discrimination measures from scores of the amount of time during the test session that each animal explores the respective objects. Preference for the novel object, demonstrated by an increase in exploration time for that item, indicates that a memory trace for the familiar object was properly encoded, consolidated and then retrieved to guide the rodent's behavior during the test session [23–28]. There are two quantitative measures that are