Behavioural Brain Research 292 (2015) 241–251

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Medial prefrontal cortex role in recognition memory in rodents

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HIGHLIGHTS

- Prefrontal cortex is required for episodic memory in humans.
- Object recognition tasks can model aspects of episodic memory in rodents.
- mPFC in rodents is required for recognition of an object in a particular context.
- mPFC might be involved in acquisition, consolidation and control of retrieval of episodic-like memories in rodents.

ARTICLE INFO

Article history:
Received 27 February 2015
Received in revised form 17 June 2015
Accepted 19 June 2015
Available online 23 June 2015

Keywords:
mPFC
Recognition memory
Object recognition
Rodents
Acquisition
Consolidation
Retrieval

ABSTRACT

The study of the neurobiology of recognition memory, defined by the integration of the different components of experiences that support recollection of past experiences have been a challenge for memory researches for many years. In the last twenty years, with the development of the spontaneous novel object recognition task and all its variants this has started to change. The features of recognition memory include a particular object or person ("what"), the context in which the experience took place, which can be the arena itself or the location within a particular arena ("where") and the particular time at which the event occurred ("when"). This definition instead of the historical anthropocentric one allows the study of this type of episodic memory in animal models. Some forms of recognition memory that require integration of different features recruit the medial prefrontal cortex. Focusing on findings from spontaneous recognition memory tasks performed by rodents, this review concentrates on the description of previous works that have examined the role that the medial prefrontal cortex has on the different steps of recognition memory. We conclude that this structure, independently of the task used, is required at different memory stages when the task cannot be solved by a single item strategy.

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http://dx.doi.org/10.1016/j.bbr.2015.06.030
0166-4328/

1. Introduction

Tulving defined episodic memory as "happenings that occur in particular places and particular times" [1]. Thus, it is not surprising that different cerebral regions have been shown to be involved in acquiring, processing, storing and using this complex type of information in order to access and retrieve a particular episodic memory. Human studies have shown that medial prefrontal cortex (mPFC), hippocampus (HIP), posterior cingulate cortex (PCC), inferiorparietal lobes (IPL), and lateral temporal cortex (LTC), are involved in episodic memory [2–16]. The analysis of the particular role of each of these regions in episodic memory is above the scope of this review. However, it is important to highlight that the mPFC has been identified in different studies as a key component of a system involved in episodic memory, independently of the studied memory phase.

The relationship between recognition and episodic memory have been debated for many years and the details of this discussion exceed the focus of the present review [17]. Briefly, some authors support that recognition memory and episodic memory are part of the same continuum [18–20]. However, other authors argued that both types of memories are related only if the process underlying recognition memory is recollection [21–23]. Independently of this discrepancies, recognition could be defined as the ability to identify if a particular event have been previously encountered [23]. In that sense, recognition memory is fundamental to our ability to record events and also to guide prospective behavior [23]. This definition of recognition memory which can be defined as the memory that allows an individual to judge the prior occurrence of a particular stimulus or episode can be studied in animal models. The first attempts to analyze recognition memory in rodents' used reward-based tasks (delay matching and non-matching to sample tasks) [24,25]. These behavioral manipulations have the drawback of requiring many training trials and as animals are often food-deprived, this could affect the motivational state and become a confound to analyze memory performance. To avoid these problems, a simpler version of a delay non-matching to sample task, the spontaneous object recognition (SOR) task [26,27] was developed. The SOR task exploits the natural tendency of rodents to explore novel stimuli over familiar stimuli. A major advantage of the SOR task is the fact that it is based in the natural preference of the animal to explore novel objects and that they are simple, less time consuming and free from stress. These characteristics, together with the flexibility to modify the task, made it the main model to study recognition memory in rodents. However, its development brought some controversy to the field [23]. Some people argued that it was not a good model of episodic memory. As has been previously reviewed episodic memory is a type of memory that involves information about temporally dated episodes or events, and temporal–spatial relations between [28,29]. Then the SOR as was initially described fell short of this definition since it only test the memory for the object per se. Even more, some authors argued that it yields in a familiarity-based rather in a recollection strategy [30,31]. This discussion is supported by the neurobiological substrates involved in the resolution of the task. A recollection strategy is supposedly relayed on the HIP, while the SOR has been heavily linked with the perirhinal cortex (PRH) but not, if at all, depends on the HIP [32] which is part of the medial temporal circuit proposed to support episodic memory in general and recollection in particular [31,33].

Nevertheless, the flexibility of the task allowed the development of different versions that take into account other features like time or context, making them a more complete animal model of what it is defined as recognition memory in humans [34–41]. The description of the different versions has been recently reviewed elsewhere [35] and is shown in Fig. 1. Briefly we describe some of the common versions (Fig. 1): Panel A: a single SOR trial consists of sample and choice phases, separated by a variable retention delay. In the sample phase, the animal is introduced into the testing apparatus, which contains two identical junk objects (i.e., X1 and X2). The animal is allowed to explore these objects for a limited amount of time before being removed from the apparatus. At the end of the retention delay, the subject is reintroduced into the apparatus, which now contains a new copy of the sample object (X3) and a novel object (Z) never before seen. Normal animals will preferentially explore the novel object in this choice phase, and this behavior is taken as the index of recognition of the familiar sample object [42]. Panel B: the Temporal memory object recognition (TMOR) implicates discrimination between familiar objects presented at different times. In this case two copies of a novel object (X) are presented and two copies of a different object (Z) are presented in the same context separated by some time, usually one hour. Then after a delay animals are re-exposed to a copy of both objects (X and Z). Rodents tend to explore more the object that was shown to them earlier and the difference in exploration between the two objects is a measure of recency memory. Panel C: the Object location (OL) task was design in order to test the ability to detect the displacement of a familiar object to a novel location. In this case during the single training session rodents are exposed to two copies of a novel object in a particular position. During the test phase, one of the copies is displaced to a new location. This change of spatial configuration triggers an increase level of exploration compared with the non-displaced copy of the object. Panel D: In the Object-in-place (OiP) task animals discriminate between familiar objects that have been previously presented. During the test phase some of these objects are switched between locations. Both locations and objects are familiar, so the novelty comes from encountering a familiar object in a familiar position where it was not previously seen. Panel E: Object-in-context (OIC) task. During the sample phase animals are exposed to two different pairs of identical objects presented in different contexts, each presentation separated by a delay. During a choice or test phase, the animals are re-exposed to one of the context containing one copy of each one of the objects seen during the sample phase thus one of the objects is "congruent" with the context and the other is not. In this task, novelty comes from a novel combination of an object and a context, and exploration will be driven by retrieval of a particular "what" and "which context" conjunctive representation. It is important to clarify that during this review we might use the term "where" in the OIC task to indicate in what context the object has been experienced ("which context"). This task has also been referred to as the "what-which occasion task" [43]. Panel F: Episodic-like-memory (ELM) task. The sample phase consists of two sessions. In each of them animals are exposed to four identical copies in a particular spatial configuration of two different objects. During the test session, animals are re exposed to two objects from each sample session. One object of each session is place in the same location while the other two objects are place in a novel location. It is expected that animals explore more the recent displaced object over the recent stationary one while the opposite pattern is expected for the older pair of objects.

Since the development of these tasks there has been a renewed interest in studying recognition memory in animal models. For that reason we will mainly review the results obtained by using them.

2. Role of mPFC in recognition memory

The mPFC in rodents is considered functionally homologous to the dorsolateral region of the human prefrontal cortex [44–47]. However, it is still on debate the homology between the human dorsolateral prefrontal cortex and rodent mPFC [48–50]. The mPFC in rats can be subdivided in two parts, the frontal area 2 and dor-