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Role of PFC during retrieval of recognition memory in rodents

Pedro Bekinschtein [a,*], Noelia Weisstaub [a,b,*]

[a] Instituto de Biología Celular y Neurociencias, Facultad de Medicina, UBA-CONICET, Paraguay 2155 3er piso, Buenos Aires (C1121ABG), Argentina
[b] Grupo de Neurociencia de Sistemas, Departamento de Fisiología, Facultad de Medicina, UBA, Paraguay 2155 7mo piso, Buenos Aires (C1121ABG), Argentina

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ABSTRACT

One of the challenges for memory researches is the study of the neurobiology of episodic memory which is defined by the integration of all the different components of experiences that support the conscious recollection of events. The features of episodic memory includes a particular object or person ("what"), the context in which the experience took place ("where") and the particular time at which the event occurred ("when"). Although episodic memory has been mainly studied in humans, there are many studies that demonstrate these features in non-human animals. Here, we summarize a set of studies that employ different versions of recognition memory tasks in animals to study the role of the medial prefrontal cortex in episodic memory.

1. Introduction

Episodic memories, the memory for specific and unique events of our life, are a main component of the bricks that help us form who we are. From human (Desgranges et al., 1998; Pergola and Suchan, 2013) and animal studies ((Clayton and Dickinson, 1998) we are starting to understand the anatomical substrates involved in this type of memories, in particular the involvement of the frontotemporal lobe and the hippocampus. However, the neurobiology underlying episodic memory in mammals is largely unknown. Over the last 30 years there has been an increase interest in understanding the neurobiological mechanisms that subserve episodic memories which lead to the development of behavioral tasks in animals that model episodic memory. Animal studies using tasks that employ a subset of episodic memory features have provided relevant mechanistic information. The first behavioral tasks developed were reward-based tasks (delay matching and non-matching to sample tasks) (Winters et al., 2008) which could have the confound of the motivational state of the animal. To avoid these problems, a simpler version of a delay non-matching to sample task, the spontaneous object recognition (SOR) task (Ennaceur et al., 1997) 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 they are simple, short and free from stress.

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 (A1 and A2). 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 (A3) and a novel object (B) never before seen by the rat. 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 (Winters et al., 2010). As mentioned, rodents naturally tend to approach and explore novel objects, which are assumed to have no natural significance to the animal and which have never been paired with a reinforcing stimulus. They readily approach objects and investigate them physically by touching and sniffing them, rearing upon and trying to manipulate them with their forepaws (Aggleton et al., 1989; Ennaceur and Aggleton, 1994). This behavior can be easily quantified and utilized to study simple recognition memory as well as more complex spatial-, temporal- and episodic-like memory in rodents. Anatomically, the perirhinal cortex (PRH) plays a critical role in object recognition (Brown and Aggleton, 2001), however other structures have also been involved (Barker and Warburton, 2011; Bussey et al., 2000; Mumby et al., 2002; Mumby et al., 2005; Kesner et al., 1993). An analysis of the literature (Forwood et al., 2005; O'Brien et al., 2006; Winters et al., 2004), suggests that

* Corresponding authors at: Instituto de Biología Celular y Neurociencias, Facultad de Medicina, UBA-CONICET, UBA-CONICET, Paraguay 2155 3er piso, Buenos Aires (C1121ABG), Argentina. Tel.: +54 115950 9500x2159.
E-mail addresses: nweisstaub@fmed.uba.ar, pbekinschtein@fmed.uba.ar (N. Weisstaub).

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the hippocampus contributes to the performance of certain object recognition tasks when spatial or contextual information becomes important (Aggleton et al., 1989; Eacott et al., 2005)

Regarding the role of the medial prefrontal cortex (mPFC), electrophysiological and lesions data suggest that this structure may also contribute to recognition memory (Barker and Warburton, 2011). Some of the features of recognition memory associated with mPFC have also been associated with the PRH. In order to address if both structures function as part of a neural network Barker et al. used a unilateral disconnection approach (Barker et al., 2007). To assess the contribution of particular brain structures to different aspects of object recognition memory process they took advantage of the plasticity that the SOR task provides. They analyzed and compared the behavioral consequences of a combined unilateral, ipsi o contralateral, disconnection between the mPFC and the PRH in 4 versions of the object recognition task (Fig. 1A–D). They used a novel object preference task, in which the rat exploration of a novel object is compared with that of a familiar object; a recency recognition task, in which the animal's ability to differentiate between two familiar objects presented at different intervals is tested; an object-in-place task, in which the animals ability to detect a particular object relative to its location and surrounding objects is examined; and an object-location task, which tests the animals ability to detect the movement of a familiar object to a novel location. They found that in the object-in-place and recency recognition tasks, the PRH, mPFC, and PRH–mPFC contralateral lesion groups showed significant memory impairments compared with the SHAM and PRH–mPFC ipsilateral groups. Only the PRH lesion group was impaired in the novel object preference task and neither group showed impairments in the object-location memory task. These results support the hypothesis that the mPFC plays a role in recognition memory in cases in which integration of object and spatial location information received from other neural regions is needed. However, the lesions did not allow discriminating at which stage of the memory process the mPFC is required.

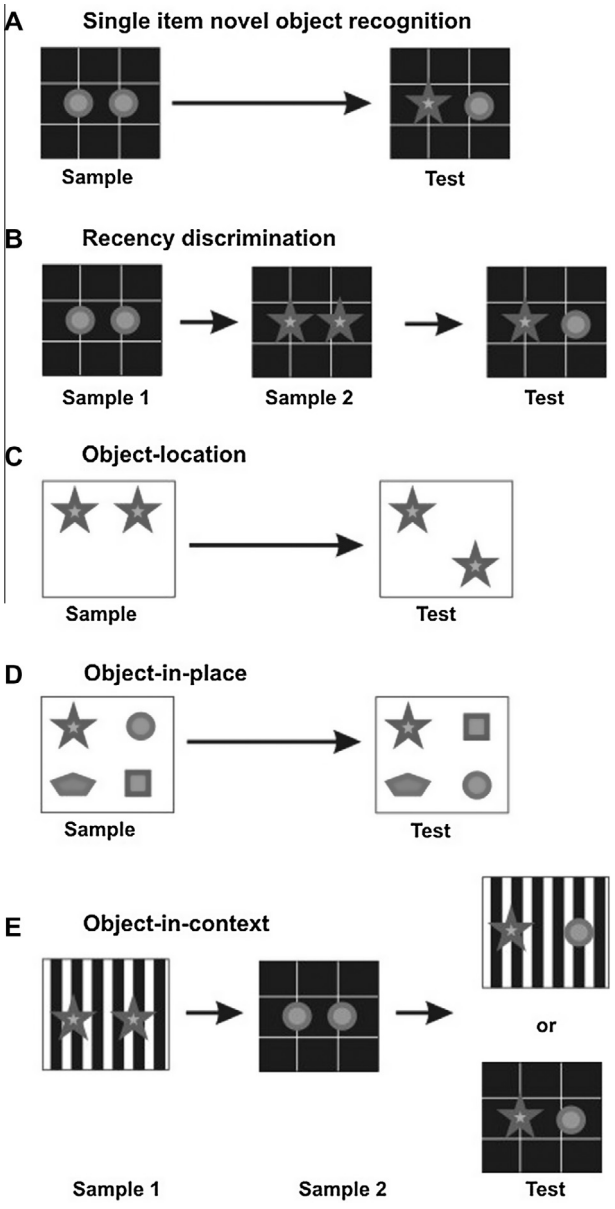

Fig. 1. Schematic representation of the different versions of the object recognition task for rodents.

Bekinschtein et al. used a pharmacological approach in order to address the role of the mPFC during retrieval of episodic memories, (Bekinschtein et al., 2013). The serotonergic system projects profusely to the mPFC. The 5-HT2A receptor (5-HT2AR) is one of the main post-synaptic serotoninergic receptor types and it is highly expressed in the PFC. A few studies in humans and animals models have addressed a potential role of 5-HT2AR in memory processes (Meneses and Hong, 1997; Wagner et al., 2008). Then the authors hypothesized that since 5-HT2AR is highly expressed in PFC, 5-HT2AR signaling in PFC could be required for accurate memory retrieval only in the cases in which the task cannot be solved using an item-only strategy and a combination of multiple elements is required. In order to address this question the authors took advantage of the ability to infuse a 5-HT2AR antagonist directly in the mPFC at a precise time point. They included, among the above mentioned tasks, another version named object-in-context (OIC) (Fig. 1E). The OIC task is a three trial procedure (Wilson et al., 2013). Rats were exposed, during the sample phase, to two different pairs of identical objects presented in different contexts. These presentations were separated by an hour. During the retention trial, carried out three hours after the last presentation, a new copy of each of the objects used before is presented in one of the contexts. Thus, one of the objects is presented in an "incongruent" context, while the other is presented in a "congruent" one. 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. Blockade of the mPFC 5-HT2AR with the 5-HT2AR antagonist MDL 11,939 fifteen minutes before the retention trial produced a significant difference in the level of exploration of both objects compared with vehicle-treated rats. As it has been shown before, vehicle treated rats showed a preference for the "incongruent" object as reflected by their increased levels of exploration of this object compared with the "congruent" one. In contrast, rats infused with MDL 11,939 showed no preference for any of the objects. This result strongly suggests that blockade of mPFC 5-HT2AR affects the capability of the animals to discriminate between two known objects that have been previously shown in different contexts. In order to control that the deficits observed in the OIC were not simply a deficit in object recognition per se, the animals were evaluated in the novel object preference task (Fig. 1A). Blockade of 5-HT2AR prior to the retention test did not affect the ability of the animals to discriminate between a familiar and a novel object. In addition, the ability to retrieve the context per se was intact, since the infusion of the 5-HT2AR antagonist into the mPFC 15 min before the retention test did not affect performance in an object-location task (Fig. 1C). The mPFC is highly involved in attention and perception processes, then the effects observed in the OIC task could be explained by a deficit in attention. To address this question, the authors used a single trial task that allow them to directly test

the possibly effect of 5-HT2AR blockade in mPFC in attention and perception. They found that independently of the infusion of 5-HT2AR antagonist into the mPFC, both groups performed equally well in this test, indicating that the effects observed in the OIC are not cause by deficits in attention and perception.

In order to understand the nature of the deficit observed in the OIC the authors performed a modified version of the OIC task in which three objects are presented. This configuration allow them to address in one experiment if the blockade of the 5-HT2AR in the mPFC produced a deficit in the retrieval of the previously known objects (both objects are seen as novel) or if the blockade allowed interference between the traces of the two known objects (both objects are seen as congruent or incongruent). Animals that receive the 5-HT2A antagonist fifteen minutes prior to the test session explored more the novel object than the other two but showed no differences in the level of exploration between the congruent and incongruent objects. Thus, single-item object recognition is unaffected by 5-HT2A blockade, but the OIC component of the task is abolished by this treatment. This means that rats remember having seen the objects, but they do not remember in which context they have seen them.

The OIC is a context-dependent task and as such requires the activation of the hippocampus. Thus, the authors wanted to know if the mPFC and the hippocampus were working as part of the common cortical network to resolve the OIC task. Then rats were implanted with cannulae in both the mPFC and the dorsal hippocampus. Hippocampal activity was block with the GABA A antagonist, muscimol, while in the mPFC they continued to use the 5-HT2A antagonist. The bilateral inactivation groups showed that both the 5-HT2AR in the mPFC and activity in the hippocampus are necessary for the correct resolution of the OIC task. To further investigate whether the interaction between the two structures is also necessary in the OIC task, they tested the MDL/Musc contralateral and ipsilateral groups. They found a deficit similar to the one observed for the bilateral inactivation of the hippocampus or bilateral infusion of MDL into the mPFC in the contralateral group but no deficit in the ipsilateral group (which leave both structure in one hemisphere intact). These experiments suggest that that the interaction between mPFC and the hippocampus is required during retrieval in the OIC task. In conclusion this work showed that activity in the mPFC is required during the retrieval of episodic memories in rodents in the cases in which the task cannot be solved by a single item strategy.

Further support to the idea that mPFC is involved in the integration of object and space information, comes from studies done by Kesner and Ragozzino (2003). The authors designed a biconditional discrimination task (pair associate), similar to a human version in which prefrontal damage has been shown to have an effect on performance (Petrides, 1982, 1997). The task required the rat to remember both object and spatial location information using a successive Go/No Go procedure. This was a rewarded task in which the animal needed to remember a combination of object and spatial location to get a reward. Two different objects and two spatial locations were used as stimuli. One object was associated with food reward in one location, but not the other and the second object had the opposite pairing. When presented with the rewarded object, the rat had to displace it and collect the reward from a food well. When presented with the non-rewarded object, no food was present and the rat had to withhold the response. The experiment involved a control group and two lesion groups, one in prelimbic and infralimbic cortices (PL–IL) and one in anterior cigulate and precentral cortices (AC–PC). While the PL–IL lesioned group failed to acquire the task, the AC–PC group learned the task at the same rate as controls. Their results support the idea that mPFC mediated working memory for objects and spatial locations.

Similar results were found by Lee and Solivan (2008) using a more sophisticated version of the biconditional discrimination task. They developed a set of behavioral manipulations that allowed the simultaneous evaluation of an object-in-place strategy and a location-in-place strategy. The authors used 4 arms of a radial maze. Two objects were presented at the end of each arm. In two of the arms, a given object was rewarded -a different one for each arm-. Thus, a correct choice involved recognition of the appropriate object and arm combination (object-in-place strategy). In the other two arms, the rule involved selecting a particular food well location, irrespective of the object. This rule required an association between two spatial variables, arm and food well location. Thus, to obtain a reward, the animals would have to use a location-in-place strategy. This study indicates that hippocampus lesions impair resolution of this task using either of the two rules. However, when muscimol was injected into the mPFC before the testing trials, performance was impaired in sham-operated animals only when they needed to use an object-in-place strategy. These results support the idea that mPFC is involved in recognition of a combination of objects and spatial locations.

Other studies have gone beyond the study of the objects in association with their locations or the objects and their temporal context. Eacott and Norman (2004) demonstrated that normal rats could differentiate objects based on their location and context, but damage to the fornix eliminates memory for the objects, their spatial position and the context in which they were experienced. Another object recognition paradigm that models certain features of episodic memory was developed by Dere et al. (2005); Kart-Teke et al. (2006). This is also a spontaneous object preference task that involves two sample phases and one test phase. The task allows the study of the "what", "where" and "when" components of episodic memory in the same test trial. Novelty can arise from the change in the identity of an object ("what" component), the change in the location of an object ("where" component) or the relative recency with which a certain object has been seen ("when" component). More recently, DeVito and Eichenbaum (2010) studied the effect of hippocampus and mPFC lesions on this episodic-like memory task in mice. They found that hippocampus lesions impaired all three components of the memory task, while mPFC lesions only affected the "where" memory component. They argue that mPFC is required for object and location associations.

The mechanisms by which mPFC can influence hippocampal memory representations to guide behavior are poorly studied. In a recent publication, Navawongse and Eichenbaum (2013) analyzed firing patterns in the hippocampus while rats performed a contex-guided object discrimination task. In this task, rats had to employ a spatial contextual rule to guide object choices. Temporary inactivation of mPFC impaired retrieval of hippocampal firing patterns that signaled specific object-location associations. After mPFC inactivation, many neurons lost object selectivity, without a change in place fields around the object sampling positions. The authors argue that their findings indicate a critical role for mPFC in top-down executive control of memory retrieval, rather than having the opposite flow of information in which mPFC would use hippocampal memories to guide behavior. This would mean that after blockade the mPFC, subjects are not able to appropriately select between competing memory traces, like during extinction (Quirk et al., 2006). During the test session, for example in the OIC task, both objects are familiar, so the rat must be able to retrieve the object-context association rather than the item-only memory trace in order to select the relevant behavior. Thus, blockade of the mPFC might result in failure to identify a specific combination of an object and a context. It is unlikely that mPFC dysfunction affects retrieval of the context only, since retrieval of an object-location task is not affected (Barker et al., 2007). This is consistent with the view that mPFC does not participate in the

spatial representation itself, but biases retrieval and selection of the appropriate contextual memory. Other possibility might be that the animals do identify the correct memory traces, but are unable to select the appropriate motor response. Although this is a possible explanation, most findings are consistent with a mechanism of memory retrieval control.

An interesting explanation could be that the animals fail at source monitoring, the ability to identify the source of remembered information (Johnson et al., 1993), for example, identifying when or where certain information was acquired. This process is suggested to be an essential part of episodic memory retrieval. Failure in source monitoring might be accompanied by misidentification of items or false memories (Farovik et al., 2008; Johnson et al., 1993). In object recognition tasks, a failure in source monitoring might be expressed as a deficit in recognition of the context in which an object has been experienced, despite this particular object still being familiar. This is consistent with the fact that mPFC dysfunction affects OIC or episodic-like memory tasks but not simple object recognition.

2. Concluding remarks

In this review we have summarized some of the research on the role of the mPFC in recognition memory in animals. Most studies support the idea that this region is involved in retrieval of object-context associations, but not single item memories. This is consistent with human data that implicates Dorso-lateral Prefrontal Cortex in recollection of episodic memories and with the role of PFC in top-down executive control. In addition, we believe that recognition memory tasks that model some aspects of episodic memory in rodents are a valuable tool to understand the neurobiological mechanisms of episodic memory retrieval.

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