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edial 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.

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.

Keywords: mPFC, recognition memory, object recognition, rodents, acquisition, consolidation, retrieval.

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 Figure 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.

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´s 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 dorsal anterior cingulate which have reciprocal connections with the somatosensory, motor and visual cortices and with temporal association cortices such as the PRH. The other subdivision includes the prelimbic (PL), infralimbic (IL) and ventral anterior cingulate cortices. These sub-structures have reciprocal connections with the PRH and entorhinal cortices, the HIP, and with the agranular insular cortex. In addition, the mPFC is connected with the medial dorsal nucleus of the thalamus (MD). The MD projects predominantly to the PL, IL and medial orbital areas in the **mFPC and primarily** transmits limbic and visceral information from the basal forebrain, lateral hypothalamus, brainstem and temporal lobe (amygdala, entorhinal, subiculum, endopiriform nucleus). Despite the differences in size and complexity, many of the same functions attributed to the dorsolateral prefrontal regions in humans are associated to the mPFC in rodents [46, 50, 51].

The mPFC is involved in temporal order, representation of egocentric space, response inhibition, behavioral flexibility, stress response and attention among other processes [52]. The first approaches to study episodic memory used rewarded tasks: delay matching or **non-matching** to sample tasks [24, 53-56]. These tasks are classical use to study different mPFC functions like working memory, reversal learning and impulsivity. Also, starting with monkeys they were modified to be able to serve as task to study recognition memory. These tasks are based on food rewarded behavior, which requires extensive training, and thus, conditioned rule learning. The task requires the animal to touch or displace the object to obtain the reward. Thus, it is probable that the animal uses different cognitive process in order to resolve it (i.e: execution of the matching or non-matching rule and the animal's ability to recognize the stimulus presented in the sample phase and guide responding accordingly in the choice phase) Also, these tasks usually involve the use of multiple trials per session. Then, a main critic is their inability to measure memory for unique events in a way that is not anticipated or expected by the animal [42, 57].

The development of novel object recognition tasks allowed the study of episodic-like memory [58] and particularly, the role of the mPFC with less confounds from other mPFC related functions, as was explained above. Several lesion studies connect the mPFC with the correct resolution of tasks that evaluate spatial memory, location memory or temporal order memory as well as more recent electrophysiological data [59]. For example, in one study, animals with lesions in the mPFC were evaluated for TMOR [41]. What the authors showed was that control rats preferred to explore the "oldest" object over the "newest" for the different time points assessed. Lesions to the mPFC affected the ability of the animal to resolve the task indicating that mPFC is involved in recency discrimination. Other studies support these findings. Using a variant of the task described above combined with a variety of pharmacological manipulations, a role for the mPFC in recency discrimination has been repeatedly seen in rats and mice [36, 38, 57, 60-63].

Barker et al (2007) found that lesion to the mPFC affects an OiP task, providing evidence that another function of the mPFC is the association of the object with the

context and place inside the context [36]. On the other hand, the same groups of animals showed no deficits in the SOR task neither they showed deficits in an OL task. These results suggested that mPFC plays an important role in cases in which integration of object and spatial location information is needed. Going a step further, De Vito & Eichenbaum (2010) analyzed the role of the mPFC in a "what, where and when" task. The version used by the authors is similar to the one described in Figure 1F. In this case during the test phase they presented the recent objects in the same place and displaced only one of the "old" objects. They saw that lesioned mice in mPFC had deficits only for the "where" but not for the "what" or "when" memories. These results are consistent with the idea that the mPFC function is important for the integration of object and location information [64]. However, the lack of deficit observed in this study for the "when" memory is a surprise based in other studies done in rats [36, 37]. The differences could have arisen from the fact that in this case the test involved the resolution of all three types of memories at once, when in other works each type of memory had been tested independently. Although the studies commented above and other lesion experiments provide important information regarding the role of the mPFC in recognition memory, one of the disadvantages of mPFC lesion models in the study of recognition memory is that it is difficult to dissect the particular memory phase(s) during which this structure is involved. One possibility to overcome these problems is by making transient lesions before or after the acquisition of the memory trace. Local and temporary manipulations of mPFC can be used to modulate the activity of this structure during different memory phases such as encoding, consolidation, retrieval and reconsolidation. During the next sections we will review a number of publications that analyze the role of the mPFC during the different stages of recognition memory in rodents.

Role of mPFC in Encoding

Encoding can be defined as the mechanism by which an experience leads to the formation of a new memory representation [12]. This phenomenon depends on the way the information is acquired. Acquisition could be incidental or intentional. Incidental is a form of unplanned or indirect learning that occurs during the acquisition of other

information, while intentional is a direct learning that is motivated and usually goal-directed. Animal studies had used both types of learning to evaluate episodic memory; however the discrimination in the object recognition task is thought to recruit incidental learning. Few studies have focus on the role of mPFC during encoding on recognition memory tasks. Kesner & Ragozzino [65] showed that the mPFC particularly the PL-IL region is involved in object-place learning. They used a modified version of a Go/No Go task. They trained the rats to associate particular objects at particular locations of a maze with a reward. They combined this task with lesions to different areas of the mPFC in rats. They found that lesions to the **PL-IL** regions impaired the acquisition of the **OiP** task. This study provided evidence to suggest that the deficit observed is due to inability to make object place associations and not to a deficit in spatial or object recognition per se.

Acquisition of recognition memory appears to depend on different neurotransmitter systems. Experiments conducted using the OiP task indicates that acquisition depends on the glutamate and cholinergic neurotransmission systems [66, 67]. In addition, the requirement of the interaction between the mPFC and other structures supports the idea that this type of acquisition requires a network in which the mPFC might be playing a top-down role [68]. Recently, the focus has been directed to the intracellular pathways that can be involved in the acquisition of recognition memories. For example, it was shown in rats that activation of PKMζ in the mPFC, but not in the HIP, is necessary for the acquisition of the OiP task. However, when they evaluated its role in the maintenance of the memory trace, they found that PKMζ activity was required in mPFC as well as in the HIP. The authors went a little further and analyzed the possible mechanism of action underneath the activation of this atypical kinase and found that during acquisition, PKMζ does not induce AMPA receptors recycling in the mPFC, which has been proposed as a mechanism of action of this atypical kinase. It is important to mention that the authors used ZIP to inhibit PKMζ activity, a pseudosubstrate peptide mimicking the amino-acid sequence of the autoinhibitory domain of atypical PKCs, then they cannot rule out that the effects observed in this work were due to the effect of ZIP on the activity of a different atypical kinase like PKCλ. Independently of the kinase involved it seems interesting that different molecular

mechanisms are recruited in different regions that conform the functional network involved in **OiP** and maybe even more interesting is that the mechanisms within a given structure differ between distinct phases of the memory process [69].

Role of mPFC in consolidation and reconsolidation

To date, it is largely believed that, in order to last more than a few hours, memory processing involves long-lasting, activity-dependent changes in synaptic strength within the neural networks activated during learning. This is supposed to be mediated by molecular mechanisms underlying functional and structural remodeling of network connectivity which in part is dependent on protein synthesis [70, 71]. This protein-synthesis-dependent phase is known as memory consolidation. However, we know now that consolidated memories, under certain conditions, can become once again dependent on protein synthesis after retrieval through a process known as reconsolidation. During reconsolidation, memories enter a labile state requiring again gene transcription changes and protein synthesis in order to re-stabilize the previously consolidated trace [71-77].

Few studies had focus on understanding the consolidation process in the mPFC during memory formation in general, and even fewer analyzed the role of this structure during consolidation of recognition memories in particular. Using an OIC task (Figure 1E). Martinez et al. (2014) disrupted the activity of mPFC using the GABA-A agonist muscimol at different time points after acquisition. They found that in the control group training on a second memory disrupted consolidation of the first one, but if mPFC activity was disrupted with muscimol 15 minutes before the second sample, only consolidation of second memory trace was disrupted leaving the first one intact [78].

Interestingly Akirav & Maroun (2006) used a SOR task (Figure 1A) to evaluate the role of ventromedial prefrontal cortex (vmPFC) during consolidation. Infusion of anisomycin (protein synthesis inhibitor) immediately after the sample phase disrupted object recognition long term memory without affecting short term memory (measured three hours after acquisition), suggesting that vmPFC is involved in consolidation of long-term memory of this task. In order to elucidate whether vmPFC was involved in reconsolidation in **SOR** memory task, twenty-four hours later animals were re-exposed

to the same sample objects to reactivate the memory trace. Anisomycin infused into vmPFC immediately after the reactivation phase was able to disrupt long-term memory suggesting that protein synthesis in this structure was also required for memory reconsolidation [74].

The studies of pharmacological manipulations mentioned above support a role of the mPFC in consolidation and reconsolidation of recognition memory. Interestingly a recent electrophysiological study also supports this function. Using mice as a model, Weible et al (2009) [79] show electrophysiological correlates of individual anterior cingulate cortex (ACC) neurons to object–place associations following short delays. As a follow up study, they modified a SOR task in order to evaluate if the ACC was also involved in consolidated recognition memory [59]. Two groups of animals were habituated to the arena but the first group had a single session to explore both objects while the second had been extensively familiarized to both objects over the course of many days. The hypothesis was that familiarization would strengthen the memory of the object-location association and that this strength would be correlated with activity in the ACC. They found that mice preferentially explore areas of the arena where an object had previously been, and that ACC neurons also respond in that location, reflecting the memory of the object/place association. These responses to absent objects were clearer for animals extensively familiarized to both objects over the course of many days. Interestingly, the correlation was still evident when mice were exposed to the absent-object arena 30 days after the last training session, suggesting that ACC neurons are involved in long term object place recognition memory.

Role of mPFC in retrieval

Retrieval is the process by which stored information can be recalled and reactivated. It has been suggested that recognition memory can be retrieved by two different mechanisms: by a sense of familiarity to a particular previously experienced stimuli or the conscious recollection of a specific stimuli [80].

The development of the different versions of the object recognition task in rodents leads to the question of what type of retrieval strategy the animals are using to resolve these tasks. It is accepted that object recognition memories are based on incidental encoding

during objects sampling, indicating that retrieval might rely on both item familiarity and event recollection [81].

Using immunohistochemistry techniques, Barbosa et al (2013) analyzed the correlation between cognitive demands and activation of structures in the network involved in recognition memory [82]. They compared the pattern of expression of two immediately early genes: c-Fos and Zif-268, after the test phase in two different recognition tasks: the SOR (Figure 1A) and an “episodic-like” memory task (what and where task) (Figure 1F). They saw that sixty minutes after retrieval the number of c-fos+ or Zif-268+ cells in mPFC were significantly increased compared to control groups, in animals exposed to the SOR task. Romero-Granados et al, **using the SOR task,** saw that the expression of **Zif-268** and BDNF in mPFC was increased 2 hours after the retrieval phase [83]. In the same way, animals exposed to an episodic-like memory task presented increased number of cells Zif-268+ cells in mPFC. These results suggest that activity within this structure is associated with successful retrieval of the task independently of the cognitive demand required.

Modulation of mPFC function and their role in spontaneous object recognition memory tasks

Glutamate

Glutamate is the main excitatory neurotransmitter in the mammalian brain. Until now, three families of ionotropic receptors with intrinsic cation permeable channels have been described: N-methyl-D-aspartate (NMDA), a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate [84]. AMPA/Kainate receptors mediate fast excitatory neurotransmission while NMDA neurotransmission is involved in the induction of synaptic plasticity, including both long-term potentiation and long-term depression [85]. For many years the main focus regarding the role of the glutamatergic system in recognition memory was its function in the PRH. Glutamate is involved in the acquisition as well as the retrieval in the PRH cortex [86-88] suggesting that this neurotransmitter

plays an important role in recognition memory. However, recently, some studies focused on its role in the mPFC. Using OiP task (Figure 1D) Barker and Warburton analyzed the role of the different glutamate receptor families [34, 66, 89]. They described a differential role for AMPA and NMDA receptors in the mPFC. Infusion of AMPA receptor antagonists (CNQX or NBQX) before acquisition impaired the performance during the test phase, suggesting that excitatory neurotransmission mediated by AMPA receptors in mPFC is necessary during learning in order to form a recognition memory trace. They expanded the study by analyzing the role of the NMDA receptor subtype. Blockade of NMDA receptors by AP5 (NMDA receptor antagonist) in the mPFC after sample phase impaired the encoding of short-term and long-term-memory. On the other hand, AP5 infusion had no effect on retrieval. These results suggest that NMDA neurotransmission is necessary for the integration of object and place information during acquisition but that during the retrieval, glutamate neurotransmission become independent of NMDA neurotransmission and relays exclusively on AMPA and kainate neurotransmission. These observations support the idea that acquisition of this type of information involved plasticity modifications within the mPFC [34, 66]. Glutamate neurotransmission in the mPFC has been implicated in the encoding and retrieval of TMOR task too. Blockade of AMPA receptos or NMDA receptors in mPFC before acquisition impairs the performance during the test phase. However, administration of AP5 before test session did not impair performance, while infusion of CNQX did, suggesting that the role of the glutamatergic system during recency discrimination in the mPFC is similar to the one observed in the OiP task [90]. Then, these results suggest that the glutamatergic system plays an important role in the mPFC in the acquisition and retrieval of mPFC dependent recognition memory tasks and even more they showed that the acquisition require NMDA dependent neurotransmission, suggesting that might involved plastic changes in this structures.

Acetylcholine

Cholinergic receptors are divided in two groups: ionotropic called nicotinic receptors, and metabotropic ones, called muscarinic receptors. The role of this neurotransmission system has been involved in different memory types in humans and animal models. In

the latest case, the focus has been mostly in aversive [91-94] but also in some forms of recognition memory [95-98]. From these studies and others emerge a clear role for this system in HIP, amygdala and PRH cortex [97].

Using OiP task, Barker et al (2009) proposed that cholinergic system was involved in acquisition of this task. Infusion of scopolamine (cholinergic muscarinic receptor antagonist) into mPFC 15 minutes before the sample phase, produce an impairment in the OiP task after either a 5 min or a 1 h delay [67].

In an effort to extend the role of the cholinergic system to other tasks, the same authors analyzed its role using the TMOR task. Infusion of scopolamine into mPFC 15 minutes before the sample phase significantly affected the performance in the TMOR task. Infusions of the same drug 15 minutes prior to the test phase had no effect. These results suggest that Acetylcholine, by the activation of muscarinic receptors is involved in the encoding, but not in the retrieval of TMOR task [90].

Serotonin

The serotonergic system consists of a group of morphologically distinct group of cell bodies located in the brain stem raphe nuclei. Although they represent a very small proportion of the total number of cells in the brain (1/1,000,000) their highly ramify axons innervate all regions of the central nervous system [99]. The 5HT cell bodies can be divided in 2: superior and inferior groups. The superior group projects mainly to the forebrain while the inferior group projects predominantly to the spinal cord, [99, 100]. The ascending projections are very extensive and contain many types of collateral innervating regions of the cerebral cortex, basal ganglia limbic system and diencephalon.

This system modulates a variety of physiological and cognitive functions and has also been link to different psychiatric disorders. It was in base of this relation that a high-order capacity to integrate behavioral functions was propose as a role for serotonin. The serotoninergic system has been linked to PFC function [101-103]. The 5-HT2A receptor is one of the main postsynaptic serotoninergic receptor types and it is highly expressed in the mPFC [104]. The role of this receptor in mPFC cellular physiology suggests that it

is important for the modulation of PFC-dependent functions. However, its role in memory processing is poorly understood. Bekinschtein et al [105] used a pharmacological approach in order to evaluate the role of the mPFC during retrieval of OIC (Figure 1E). 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. Infusion of a selective 5-HT2A receptor antagonist (MDL 11,939) 15 minutes before the retention trial into the mPFC produced a significant difference in the level of exploration of both objects compared with vehicle-treated rats. Using the same pharmacological approach, the authors showed that blocking 5-HT2A receptors activity in the mPFC had no effect in the **OL** or novelty recognition per se. However, when the animals were exposed to a **TMOR** task, infusion of MDL 11,939 before the retention test, produce a deficit similar to the one observed in the OIC. The **TMOR** and OIC tasks have in common that they require integration of different types of information: recency in one case and contextual in the other. The fact that both tasks were specifically affected suggests that mPFC activity and particularly, modulation of this structure through 5-HT2A receptors are necessary when the task cannot be resolved by a single item strategy.

Although 5-HT2A receptors are one of the most important receptors expressed in the mPFC they are not the only ones. Other receptors excitatory and inhibitory are also expressed in this region [103] and in some cases they are co-expressed with 5-HT2A receptors. In order to evaluate the possible role of other receptors in the modulation of mPFC activity during recognition memory the authors used the OIC task. The effects of selective 5-HT2C receptors antagonist or 5-HT1A receptors agonists were assessed. Infusion of 5-HT2C antagonist before the retention test produced no deficit in the OIC test suggesting that serotonin does not require activity of this type of receptors to modulate mPFC function during this task. On the contrary, activation of 5-HT1A (5-HT1A receptors are coupled to G protein) before the retention test produced a deficit in the OIC task similar to the one observed with MDL 11,939. These results suggest that both types of receptors, 5HT2A and 5HT1A might play a role in the serotonergic modulation on mPFC activity during retrieval.

Dopamine

Dopamine (DA) is an important neuromodulator of mPFC function supported anatomically by the rich innervations of DA fibers originating in the ventral tegmental area that reaches the mPFC [106].Consistent with this anatomical connection, DA modulation within mPFC has been shown to play an important role in regulating working memory, delayed alternation, attention, cognitive flexibility, learning and memory as well as other cognitive functions [107-110].

Few studies have focus on the role of the dopamine system in recognition memory. Systemic administration of a D1 r**eceptor** agonist [111] and genetically modified mice for the D4 receptor subtype [112] provided the first evidences indicating that dopamine plays a role in recognition memory as measured in different behavioral tasks.

Lesions of dopaminergic fibers in the mPFC could be achieved by infusion of the selective neurotoxin 6-OHDA. Using this technique Nelson et al. **(2011)**, evaluate the role of dopaminergic neuromodulation in different regions of the mPFC across novel object recognition variants. They found that DA neurotransmission plays a role in the PL and IL region of the mPFC in the TMOR task. Anatomical analysis of the neuromodulation of DA suggests that the catecholamine depletion within the PL is sufficient to impair discrimination in the TMOR [113]. Using a similar strategy Chao et al (2013) showed that contralateral and ipsilateral lesions in mPFC and the medial forebrain bundle (collection of long axons that include dopaminergic nigrostriatal fibers) impairs the animal´s performance in OL task and OiP [114]. Interestingly, contralateral lesions between the medial forebrain bundle and the mPFC affects the performance in the SOR. Medial forebrain bundle lesion affects dopaminergic levels in the striatum and nucleus accumbens. Anatomically the basal ganglia is tightly connected with the mPFC [115]. Thus, it is not surprising that interaction between these structures have been shown to play a role in object recognition processing [29]. This particular lesion study supports a role for the dopaminergic neurotransmission in object memory processing. As well as with other neuromodulators, dopaminergic complexity comes from the expression pattern and signaling of the different types of receptors. The role of the different types of dopamine receptors in the modulation of SOR task was evaluated in two independent studies. In the first study the infusion of L741626 (D2 receptor

antagonist) pre-training produce a deficit in the SOR task, measured 30 minutes after the training session. In the second study the authors injected SCH23390 (D1 receptor antagonist) pre-training and found a deficit in the test phase 24 hours later but not an hour later, suggesting that D1 receptors are required for long-term but not for the acquisition or the expression of short-term memory of the SOR task. Interestingly, in the same study the microinfusion of raclopride, a D2/D3 **receptors** antagonist had no effect [116, 117]. These results were surprising in the light of the strong bibliography indicating that mPFC is not involved in the resolution of the SOR task. However, these effects could be better explained as driven by reward/attentional mechanisms rather than an effect on memory per se.

Supporting this finding, a recent study by Savalli et al (2015) showed that the selective blockade of D1/D5 receptors in mPFC 5 min or 1 hour before the sample phase disrupts OiP performance [118]. Interestingly, D1/D5 neurotransmission does not appear to be involved in the retrieval of the OiP memory since the infusion of the drug before the test had no effect. Importantly, in this case, the effect could not be attributed to a general impairment in arousal or attention because when the infusion of the D1/D5 receptor antagonist into mPFC was done 5 min or 1 hour before the sample phase of the OL task or SOR task there was no evidence of memory impairment. This study showed a selective requirement of D1/D5 receptor activity in the mPFC during the sample phase OiP task, suggesting that D1/D5 signaling could be involved in plasticity processes necessary for object-place associations.

Dopaminergic modulation of the mPFC function is particularly important since disturbances in the dopaminergic system has been linked to psychiatric disorders like schizophrenia [119-124] which includes deficits in memory and cognition. A recent study by De Bundel et al (2013) analyzed the role of D1/D5 receptors in the mPFC in recognition memory under the hypothesis that D1/D5 signaling modulates long-term recognition memory. In order to test this, they infused SCH23390 or SKF81297(D1/D5 receptors agonists) into mPFC before training rats for 2 or 15 minutes in the SOR task. They saw that the animals infused with SCH23390 and exposed for 15 minutes presented lower discrimination indexes than the control group for the same exposure time. But if the animals was infused with SKF81297 and exposed for 2 minutes to the

objects, they presented a higher discrimination index compared to the control group [125]. This result suggests that the activity of this DA receptors in the mPFC is required during the acquisition of this type of recognition memory. The authors went a step further and analyzed if f D1/D5 receptors signaling might be part of the mechanism of action of reboxetine (an antidepressant that block the norepinephrine transporter). To elucidate this hypothesis, they made systemic administration of this drug, and made infusions of SCH23390 into mPFC before a 15 minutes sample phase. They saw that the infusion of the D1/D5 receptors antagonist impaired the performance during the test phase in contrast to the group that received reboxetine systemically and infusions of vehicle into mPFC. These results suggest that the modulation of DA system, specifically D1/D5 receptors, could be one of the mechanisms modulated by some drugs that presents memory enhancing effects.

Dopamine (DA) is a likely neuromodulator of mPFC function in that the region is richly innervated by DA fibers originating in the ventral tegmental area [106]. One of the functions proposed for the mPFC is a role the consolidation of long term memory, then; it is plausible that dopaminergic modulation of mPFC might play a role in this process. To test this hypothesis, Rossato et al (2013) blocked the VTA immediately post training by infusing muscimol or blocked NMDA receptors by infusing AP5 and found a deficit in long-term memory for the SOR task. In order to evaluate the regulatory role that different DA receptors have in this process, they performed post-training infusions of SCH23390 into mPFC as well as other structures part of the mesocorticolimbic circuit: the amygdala and HIP. The inhibition of the D1/D5 receptors in the mPFC but not D2 receptors post-training affected the consolidation of the SOR memory [126].

The authors went a step further and decided to look at the interaction between some of the structures that are part of the mesocorticolimbic circuit. Since blocking DA neurotransmission from the VTA disrupts the consolidation of the SOR memory, they decided to evaluate which structures were involved in this process. By using simultaneous injections they found that the deficit observed by blocking the VTA could be rescued by the co-activation of D1/D5 receptors in the amygdala and mPFC but not

the HIP-mPFC, suggesting that there is a functional connectivity between these two structures necessary for the consolidation of SOR memories [126].

Interactions between mPFC and other structures

In the last few years, some studies have proposed that mPFC interacts with the HIP and/or the PRH during the resolution of different types of recognition memory tasks. The quality of these interactions would depend on the features evaluated by the task [35, 77, 127 for review]. Using anatomical tracing techniques, connections between mPFC, HIP and PRH have been found in monkeys and rats [34, 128-138, 139 for review]. Several studies indicate that the HIP is involved in recognition memory when resolution of the task depends on the processing of contextual information [60, 68, 140-144] while PRH is crucial for recognition memory as it provides information about the objects, their features and familiarity discrimination [25, 145, 146]. Disconnection experiments are a useful tool to analyze the functional interaction between structures that are hypothesized to participate in a particular function. By making ipsilateral or contralateral lesions a functional role between the structures can be manifested. The effect observed with this type of manipulations should be analyzed taking into consideration the anatomical connection between the structures. The lack of an effect in a disconnection study could indicate that the structures instead of being part of the same network might be working **as** parallel networks.

HIP and PRH are the other main structures analyzed in relation with recognition memory. Then the disconnection studies have mainly focus on the interactions betweente these structures. Studies using ipsilateral and contraleteral lesions involving the mPFC support the role of this structures in some forms of recognition memory. Contralateral lesions in mPFC-HIP show impaired performance in the OiP memory task compared to the ipsilateral lesioned group. Similarly, mPFC-PRH contralateral lesions showed deficits in the OiP and TMOR tasks [36]. Similar results were obtained if the contralateral lesions were made between the HIP-PRH [142] suggesting that these regions interact during recognition memory tasks that require the integration of object and contextual information for its resolution. Authors conclude that each of these neural regions could be included in a network necessary to process different types of

information. HIP could be processing spatial information, while PRH would be processing the information of the object identity [32, 36, 145, 147-150] and the mPFC would be involved in the formation of association between object and spatial information [142].

Aggleton and Brown (1999) proposed the **MD of the thalamus** as a structure involved in a larger neural network necessary for item recognition. **The network proposed** was centered on the PRH and includes the mPFC too [30]. To elucidate if the MD **in the** rat was involved during single item recognition Cross et al (2013) made lesions in mPFC and MD and exposed animals to the OiP and TMOR tasks. They saw that mPFC-MD contralateral lesion impaired the performance in both tasks. On top of the relation between the different structures, different groups have recently started to analyze the modulatory role that different neurotransmission systems have in the interaction between mPFC and other structures [151]. Using the OiP task, Barker & Warburton (2013) made contralateral and ipsilateral infusions of NBQX or AP5 into **mPFC-HIP or HIP-PRH** in order to elucidate if the glutamatergic system was involved in the functioning of this network during acquisition and retrieval. They found that blocking AMPA receptors in contralateral **mPFC-HIP or HIP-PRH** impaired the performance of animals treated before acquisition or retrieval. On the other hand, contralateral infusions of AP5 in mPFC-HIP or HIP-PRH impairs acquisition but not retrieval on this task [68]. However infusions of AP5 or scopolamine before the test phase impaired discrimination, suggesting that glutamate as well as cholinergic neurotransmission play a role in the different phases of recognition memory [66, 67]. In addition, contralateral infusion in mPFC-PRH of CNQX (AMPA receptor antagonist), AP5 or scopolamine during the encoding phase of the TMOR task present an impairment during the test phase [90].

Other recognition memory tasks were also used to evaluate the network involved in these types of tests. The OIC task is a context dependent task so Bekinschtein et al (2013) wanted to test if the HIP and the mPFC were working as part of the same network during the retrieval of this type of task. To test this, rats were implanted with cannulae in both the mPFC and the dorsal HIP. Hippocampal activity was blocked with muscimol, while in the mPFC they selectively blocked 5-HT2A receptors. The bilateral

inactivation groups showed that both the 5-HT2A receptor in the mPFC and activity in the HIP were necessary for the correct resolution of the OIC task. To further investigate whether the interaction between the two structures was also a requirement, they tested the MDL/Musc contralateral and ipsilateral groups. Similar to the bilateral inactivation of the HIP or bilateral infusion of MDL, they found a deficit in the contralateral group but no deficit in the ipsilateral group (which leaves both structures functional in one hemisphere). These experiments suggest that the interaction between mPFC and the HIP is required during retrieval in the OIC task [105].

Conclusions

In this review we summarize a body of work that supports a role for the mPFC in recognition memory in rodents. Most of the studies provide evidence for a participation of this structure in the different phases of recognition memory, particularly when the task used requires the integration of different features but not when it can be solved by a single item strategy. This idea is also supported by the particular cases in which the mPFC participates in the NOR task, since there is evidence for a requirement only if the NOR version used involves the acquisition of two different objects instead of two copies of the same item.

The mPFC has been consistently related to executive functions and it is possible that some of its roles in recognition memory can be grouped into these types of cognitive processes. Most of the studies showed that the mPFC interacts with other structures that are part of a network involved in recognition memory. Then the most plausible role for this structure as one of the higher order in the network is to exert top-down control over the other structures involved. As it was mention before, the mPFC is engaged when the task cannot be solved by a single item strategy. Then, this structure could be involved in the integration of different features into a single unitary construct. We can think that this function could be separated in at least, two different processes that might take play simultaneously. On one hand the integration of the relevant information to form a congruent memory of the event in place. On the other hand it might inhibit the integration of other information that might be present and that is less relevant, into the same construct. How the mPFC can exert control over other structures and the

mechanisms involved in the interaction between them are not fully understood yet. It is also possible that the role of the structure might change during the different steps of the memory process. mPFC appears to be involved in every memory phase, from the acquistion to the retrieval of these complex recognition tasks. During acquisition, one role of the mPFC could be to increase attention to the novel situation. However, it is also possible to think that some of the information is consolidated and stored within the PFC to be used later as an index to effectively control the retrieval of the correct memory trace. There is little information on how the mPFC might control retrieval. Different mechanisms have been proposed, such as inhibitory control, decreasing the level of interference or source monitoring. For the moment, what is clear is that the mPFC is important for recognition memory, but how and exactly what is doing is still far from being understood. **To get at least a hint** of it, we might required the use of novel techniques that could allow researchers to have a rapid and tight control over the activity of the structure during the different memory phases.

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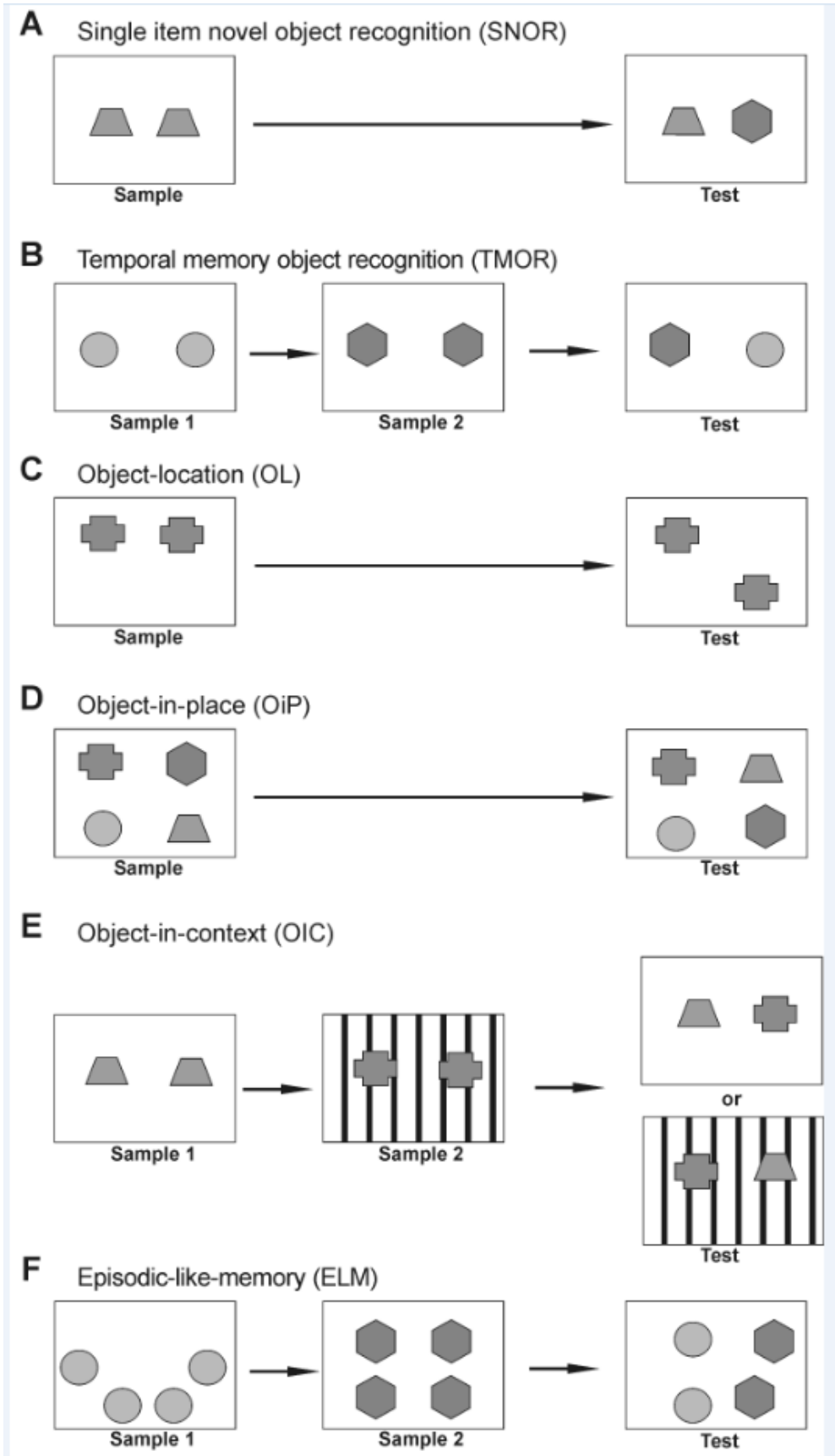
Figure Legend:

Figure 1: Schematic representation of the different versions of the object recognition task for rodents



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