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The medial prefrontal cortex - hippocampus circuit that integrates information of object, place and time to construct episodic memory in rodents: behavioral, anatomical and neurochemical properties

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Abstract

Rats and mice have been demonstrated to show episodic-like memory, a prototype of episodic memory, as defined by an integrated memory of the experience of an object or event, in a particular place and time. Such memory can be assessed via the use of spontaneous object exploration paradigms, variably designed to measure memory for object, place, temporal order and object-location inter-relationships. We review the methodological properties of these tests, the neurobiology about *time* and discuss the evidence for the involvement of the medial prefrontal cortex (mPFC), entorhinal cortex (EC) and hippocampus, with respect to their anatomy, neurotransmitter systems and functional circuits. The systematic analysis suggests that a specific circuit between the mPFC, lateral EC and hippocampus encodes the information for event, place and time of occurrence into the complex episodic-like memory, as a top-down regulation from the mPFC onto the hippocampus. This circuit can be distinguished from the neuronal component memory systems for processing the individual information of object, time and place.

Keywords

entorhinal cortex; episodic memory; CA1; CA3; prefrontal cortex; object recognition

1. Introduction

Episodic memory is conceptualized as recollection of an unique event together with the time and place of its occurrence. Endel Tulving proposed *episodic memory* as a hypothetical

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memory system for specific personal experiences, that are “consciously” remembered, encompassing *what* happened *where* and *when*, thus, entailing a kind of “mental time travel” (Tulving, 1983; Tulving, 2002). Since the emergence of this concept of episodic memory, there has been an active debate as to whether nonhuman animals (referred as animals herein) possess this type of memory, particularly because of anthropocentric concepts such as “consciousness” and “mental travel” that have been used to define it. The past two decades studies have revealed new insight on this question with evidence that animals can show a memory akin to human episodic memory, with arguments based on evolution, neuroanatomy and neurobiology (Allen and Fortin, 2013; Fortin et al., 2004; Manns and Eichenbaum, 2006; Templer and Hampton, 2013). These perspectives propose that similar neuroanatomical and neurobiological substrates of memory systems are shared by different species with humans, including a prototype of “episodic memory” which can be studied in animal models to decipher its neurobiological mechanisms.

The pioneering work by Clayton and Dickinson demonstrated the retrieval of specific experiences in animals. Scrub jays were trained to find different food based on their distinct locations and the time when they were confronted. The jays were able to learn that two kinds of foods (what) were placed separately in two different locations (where) and that, dependent on a short or a long delay (when), one of the foods became non-palatable. With this combination of what-where-when components, the authors operationalized the components of episodic memory into observable behavioral terms in an animal model and termed it “episodic-like memory” (Clayton and Dickinson, 1998). Such episodic-like memory (sometimes termed “what-where-when” memory) has been accepted to be a prototype of episodic memory and has been studied in many species (Allen and Fortin, 2013; Binder et al., 2015; Crystal, 2010; Dere et al., 2006; Ergorul and Eichenbaum, 2004; Fugazza et al., 2016; Hamilton et al., 2016; Templer and Hampton, 2013). Cognitive psychologists and neuroscientists also study the nature of episodic-like memory and compare it with episodic memory in humans (Holland and Smulders, 2011; Zlomuzica et al., 2016). Episodic-like memory paradigms have also been adapted to investigate episodic memory in young children, given that they cannot clearly express their experiences with words (Clayton and Russell, 2009; Russell et al., 2011).

There are principally two methodological approaches in the studies of episodic-like memory in animals, namely *training-based* and *training-free* models. The training-based models are directly related to the study of Clayton and Dickinson (1998). With this approach, animals are gradually guided to learn certain “what-where-when” rules with the help of positive and/or negative reinforcement. For instance, Babb and Crystal (2006) designed a paradigm to test whether rats remember a specific experience. Regular rat chow and flavored pellets, e.g. grape and raspberry, were placed separately in the ends of four of eight arms of a radial-arm maze, with the other four arms being blocked. Then, a short or a long delay decided what kinds of pellets were available and in which arms they were placed. After a short delay, all arms were accessible and regular chow pellets were placed in the previously blocked arms (no flavored pellets were involved). If a long delay was applied, all arms were accessible, with regular chow pellets placed in the previously blocked arms and the flavored pellets now available in the previously baited arms. Rats revisited the flavored-baited arms more often after a long delay than after a short delay, indicating that they acquired a specific

"what-where-when" memory (Babb and Crystal, 2006). Some paradigms have used an odor-span task (Dudchenko et al., 2000) by presenting different odor stimuli placed at distinct contexts or locations across several time delays (Branch et al., 2014; Ergorul and Eichenbaum, 2004). Fear conditioning has also been used to assess episodic-like memory in rats by Li and colleagues (2011), who exposed animals to two distinct contexts at different times of the day - to one context in the morning and the other in the afternoon. They were then given light electrical shock in a different context, either in the morning or in the afternoon. One day after this contextual conditioning, specifically at noon, they were placed back into one of the contexts that had not been paired with electrical shock. Thus, the animals learned to avoid cues for the time point and context of the punishing stimulation. They found that rats exhibited more freezing behavior (indicating fear) in the context that was paired congruent to the time of shock delivery than in the context that was presented incongruent with time of shock application (Li et al., 2011). Similar results were found in an earlier study (O'Brien and Sutherland, 2007). Using classical conditioned licking behavior, Veyrac and colleagues (2015) designed a complicated task demanding rats to learn two odor-drink associations (*what*) in different locations (*where*) within two different multisensory enriched environments (in which context/occasion it happened). They found that rats were able to recollect accurately such episodic-like memory for at least 24 hours (Veyrac et al., 2015). In other experiments rats were trained to remember a specific olfactory memory in context and demonstrated their ability to form and recall episodic-like memory (Panoz-Brown et al., 2016; Panoz-Brown et al., 2018). Although training-based models can be interpreted in terms of the expression of "what-where-when" memory, such training procedures can be argued to involve learning about facts (semantic memory), rather than about specific experiences (episodic memory). To overcome this critique, the Crystal laboratory developed a brilliant task to train rats to answer an unexpected question, which mimics a common characteristic of episodic memory in daily life for incidental encoding and unexpected retrieval. Rats were demanded to forage foods in a non-match to sample task (i.e., foods were located in previously non-visited places) and in a response-based T-maze task (i.e., if a sample of food was given in the start arm, turn left; otherwise, turn right), with both tasks being conducted within the same radial maze. After learning the rules of both tasks, rats were asked to retrieve memory of an earlier event that was encoded incidentally: A sample of food was given, or not, in the learning trial of the non-match to sample task, followed by the T-maze test trial. Their findings indicate that rats can answer such a question and that this performance is hippocampus-dependent (Zhou et al., 2012). One of the features of training-based models is that it is time-consuming to train animals and that "emotional" factors (e.g. anxiety/fear reactions to aversive stimulation, incentive/reward-based motivational responses) are likely involved in order to motivate animals to acquire the necessary level of learning. Therefore, in such training-based models the neurobiological system of episodic memory is likely to converge with the amygdala and/or nucleus accumbens for coping with anxiety/fear and/or incentive motivation, respectively.

In contrast, *training-free models* endeavor to eliminate the application of training altogether, and are designed to decrease or avoid the involvement of emotional and motivational variables (e.g. food restriction or punishing stimulation) and to employ measures that are related to the innate nature of animals to behave in a "what-where-when" setting. For

example, Fellini and Morellini (2013) designed a test, which involves different social conspecifics (a female C57BL/6J mouse and a male CD-1 mouse) that are presented at different locations and time points. They found that male C57BL/6J mice approached and avoided the locations that were previously associated with the female C57BL/6J mouse or the male CD-1 mouse, respectively, according to the temporal cues related to social conspecifics (Fellini and Morellini, 2013). Likely, the presence of social stimuli engages brain circuits for the processing of social approach and avoidance behaviors, such as the amygdala.

Alternatively, *spontaneous object exploration* in rodent studies of recognition memory is a well-established training-free animal model. This test is based on the natural tendency of many species to explore novel stimuli. For example, the length of time spent on exploring a novel object is compared with the time engaged in exploring a familiar object. The difference between the duration of exploration of a novel versus familiar object can be taken as an indication for memory, by the argument that animals tend to explore novel objects more because they remember the familiar ones (Ennaceur and Delacour, 1988). Caution must be exercised to rule out confounding interpretations, such as the absence of preference for a given object, fear of novelty, hyper- or hypo-locomotor activity, sensorimotor malfunctions and others. These factors can be monitored before and during the tests. Spontaneous object exploration can be used to assess memory for “what” (novel object preference; NOP) (Ennaceur and Delacour, 1988), for “where” (object place preference; OPP) (Ennaceur et al., 1997), and for “when” (memory for temporal order or recency; TOM) (Mitchell and Laiacona, 1998). A direct way to measure episodic-like memory is to combine the three “what”, “where” and “when” object exploration tests into one integrated paradigm (this test was first developed for rats (Kart-Teke et al., 2006) and then adapted for mice (Dere et al., 2005b). In this test, two sets of four objects (*what*) are placed at different locations (*where*), whereby the temporal appearance of each set of objects is also different (*when*). Based on the experimental model, episodic-like memory has been found to be not simply a combination of “what”, “where” and “when” memories, but a meta-system which integrates these three components into a complex and distinct compound system (de Souza Silva et al., 2016).

Following the same principle of combining the NOP, OPP and TOM tests, various episodic-like memory paradigms were developed (Davis et al., 2013a; Davis et al., 2013b; Good et al., 2007a; Good et al., 2007b). For example, two distinct objects were presented, followed by another two distinct objects at different locations, and then all the four objects were placed, while the object-locations of one of the two objects from each temporal set was interchanged. As a result, the characteristic of each object applied is determined by *what* type of object, *when* it was shown and *where* it appeared, similar to the Kart-Teke et al paradigm (2006). Recently, Barker and colleagues exploited this variant of episodic-like memory test and found important neurobiological correlates to episodic-like memory (Barker et al., 2017) (see section 4.2).

Here we will detail the properties of spontaneous object exploration paradigms, the NOP (*what*), OPP (*where*) and TOM (*when*) tests, and the integrative episodic-like memory paradigms. We will focus on the evidence primarily found via training-free models in

rodents and propose a working hypothesis that identifies the medial prefrontal cortex (mPFC), lateral entorhinal cortex (LEC) and hippocampus as key brain substrates of a neuronal network that subserves episodic memory. The neurotransmitter systems within the mPFC and hippocampus are crucial for the processing of memory and will also be discussed. We will primarily refer to the articles published after 2007 since the findings of NOP, OPP and TOM tests have been summarized (Dere et al., 2007). "Context"-manipulated object exploration tests, e.g., the *What-Where-Which* test (Davis et al., 2013b; Eacott and Norman, 2004), will not be reviewed. We consider that this topic is worthy to be discussed in a separate article, since it has been actively studied and debated in concept and experimental definition of context, particularly in the *context* (source) of episodic memory.

2. Basic concepts and methodological factors for measuring object-, place-, time- and episodic-memory based on object exploration

2.1. Novel object preference (NOP)

The term "novel object preference (NOP)" applies to the situation where an animal spends more time exploring a novel object than a familiar one. The NOP test has become one of the most frequently used behavioral paradigms in the fields of neurobiology, psychopharmacology and behavioral neuroscience in the past two decades (Ennaceur and de Souza Silva, 2018).

The NOP test are said to utilize no obvious positive or negative reinforcer and to be dependent on the natural tendency of rodents to explore novel objects more than old ones (Berlyne, 1950; Ennaceur and Delacour, 1988). However, all behaviors are "motivated" and guided by positive and negative outcomes (reinforcers). One can argue that the exploration of novelty is likely motivated by the possibility of a potential source of reward, i.e., positive reinforcement, but also by negative reinforcement, such as escape from boredom and reduction of anxiety/fear, in the case it turns out to be that the novel object is not dangerous or threatening, i.e., has a benign outcome. Novel object exploration might also be influenced by motivation for social interaction (with the object) or by novelty seeking; i.e., novelty *per se* being a reinforcer. Conversely, animals may fear a novel object, and a neophobic animal might explore less, without necessarily meaning that it does not remember. A change in NOP resulting from a brain lesion, pharmacological challenge or genetic manipulation could, therefore, be a consequence of action on any of these potential variables that can influence object exploration. These variables have not been earnestly considered in the literature using the NOP test.

In rodents, the classical design of the NOP test involves a sample/encoding/learning trial and a test/retrieval/recall trial, separated by a time delay/retention interval. During the sample trial, two identical objects are presented in a testing arena (usually an open field to which animals are previously habituated). In the test trial, one of these is replaced by a novel unknown, but comparably preferred, object (Fig.1A, top). Since two distinct objects are presented in the test trial, their locations should be counter-balanced between subjects to minimize the possible bias of object-location. A preference for exploring the novel object over the familiar one indicates memory of the familiar object that was previously explored in

the sample trial. The time differences between the exploration of familiar and novel objects are subtracted and used for the binary judgement of the object memory. Details about how to measure, calculate and perform statistics for the exploration differences can be found in these articles (Akkerman et al., 2012a; Akkerman et al., 2012b). The popular nomenclature of this paradigm, “novel object recognition”, somehow misrepresents the concept of this test, since, instead of recognizing the novel object, the one recognized is the familiar one (Ennaceur, 2010). A term such as “novel object preference” or simply “object recognition”, for exploring the novel object better reflects that the underlying memory is for the previously explored object.

Notwithstanding, some researchers apply two distinct objects in the sample trial of the NOP paradigm (Fig.1A, bottom). Compared to the application of identical objects, that of distinct objects is likely to involve not only novel object identity, but also inter-object relationship (Arain et al., 2012), which presumably activates brain regions for the processing of object-object and/or object-context association more than that for object identity. Not many studies have tried to differentiate the underlying mechanism of the NOP test with applying identical objects in the sample trial from that with distinct objects. When two distinct objects were placed in one context, followed by presenting two copies of one of the familiar objects in another new context, rats showed object preference according to the local cues, but not the spatial ones (Poulter et al., 2013), implying that animals were able to remember the relationship between distinct objects. Animals could recognize them as changes of local features, which has been shown to impact object recognition in animals with lesions on the hippocampus (Piterkin et al., 2008) and LEC (Kuruvilla and Ainge, 2017). In the object-location recognition test in which two distinct objects were presented, followed by two identical objects chosen from either the previously used ones, the LEC lesioned rats showed deficient performance, but not in the NOP test (Wilson et al., 2013c). Although the object-location recognition test measures whether animals remember the location of the changed object, it could potentially also be involved in the memory for the change of inter-object relationship (recognition on the alteration of local features). In a study of disconnecting mPFC and LEC, the memory tested by the NOP test with identical objects was intact, but not when distinct objects were applied during the learning (Chao et al., 2016a). Similarly, deficits were found in LEC lesioned rats when four distinct objects, but not when four identical objects, were presented to be learned (Rodo et al., 2017).This suggests that the recognition memory for identical objects is not as the same as the memory for distinct objects.

Rodents not only use the eyes, nose and forelimbs but also their mechanosensitive whiskers during object exploration (Sofroniew and Svoboda, 2015), and thus, the memory for objects is constructed by a convergence of multiple sensory systems. To study how different sensations contribute to object recognition memory, researchers have tried to dissect the visual (by presenting objects behind transparent barriers, which prevents physical contact), tactile (by presenting objects under red light, which masks the animals’ vision) and visual-tactile interaction (tactile condition for learning, followed by visual condition for testing, or *vice versa*, called cross-modal object recognition; CMOR) effects (Winters and Reid, 2010). This and related issues (Hu et al., 2018) have been studied by a series of systematic experiments based on the CMOR test (Gaynor et al., 2018; Jacklin et al., 2016; Jacklin et al.,

2012; Jacklin et al., 2015; Paylor et al., 2018; Reid et al., 2012, 2014). The interaction between sensations and object recognition is an important topic, but will not be addressed here as it is beyond the scope of this review.

The NOP paradigm has sometimes been called and used to assess “episodic-like memory”, partly due to the conceptual similarity between the memory systems of recognition memory and of episodic memory. Although NOP processing could be involved in episodic memory, at least in the property of “what”, NOP memory does not necessarily demonstrate the properties of “where” and “when”. Thus, the NOP test, *per se*, is not an appropriate measurement of “episodic-like memory”.

2.1.1. Factors influencing performance—Here we only discuss the methodological factors of NOP. Factors that directly influence the biological states of experimental animals, such as species (Stranahan, 2011), strains, colony conditions, gender (van Goethem et al., 2012), stress (Eagle et al., 2013; Li et al., 2012; Nava-Mesa et al., 2013), early experience (McLean et al., 2010; Plescia et al., 2014), diet (Beilharz et al., 2014; Sarfert et al., 2017) etc., are not in the scope of this review.

Similar to many other behavioral paradigms, any factor involved in either one of the NOP procedural steps can influence the outcome. One factor is the habituation to the testing arena which is used to reduce anxiety and arousal levels of animals (Okuda et al., 2004; Roozendaal et al., 2006). Animals which were not habituated to a testing environment had a twofold higher plasma corticosterone level (Okuda et al., 2004) and displayed more anxiety-related behavior in the open-field test (Maroun and Akirav, 2008) compared to habituated ones. NOP memory tested 24 hours later was found to be disrupted in the non-habituated, but not in the habituated animals (Maroun and Akirav, 2008). Interestingly, exposure to a stressor (30 min on an elevated platform with lights) immediately after the sample trial of NOP, reversed the effects on the habituated and non-habituated animals (Maroun and Akirav, 2008). This suggests that the initial level of arousal (related to habituation versus non-habituation) interacts with the stressor following the learning and influences NOP consolidation. Habituation to the testing environment, which reduces novelty-induced arousal or anxiety, directly contributes to memory for objects. Thus, a habituation procedure is important for NOP testing (Yi et al., 2016) and should be conducted unless experiments are designed to test stress-related issues. In the same vein, any treatment which causes deficiency in habituation learning, such as lesion, pharmacological administration, gene knockout, opto- and chemogenetic manipulations etc., should be considered as a confounding factor when NOP performance is impaired. The procedure of environmental habituation varies among different laboratories, such as absence or presence of objects inside the testing arena (Besheer and Bevins, 2000). For pharmacological experiments, vehicle injections during habituation are suggested, as studies have shown that the first-time injection increases the duration of exploratory activity (Akkerman et al., 2012a).

The degree of habituation learning can be examined by behavioral changes in either within or between sessions (Schildein et al., 2002; Thiel et al., 1998) and used to determine whether a manipulated experimental factor influences the process of habituation.

The second factor is the duration of exploration of objects. In the classic NOP test in which two identical objects were used, studies have shown that a minimum duration of object exploration (reach 10–20 seconds in rats and mice) is essential for testing NOP, both in the sample and test trials, in order to decrease large variation in the test trial (Akkerman et al., 2012a). Once the minimum amount of exploration is reached, the level of exploration in the sample trial is not correlated with the performance in the test trial (Akkerman et al., 2012a; Gaskin et al., 2010). The duration of object exploration is associated with the nature of the objects. The qualities of the objects, e.g. weight, shape, size and texture, should be well-controlled and odors from objects themselves or from animals between trials should be avoided. Objects should be heavy enough to prevent from being moved by the subjects. Any object that incurs significantly higher, lower or no exploration should not be used. Objects made of glass or porcelain are recommended since they can be easily and well cleaned. Objects that can or cannot be climbed by animals have similar but subtle effects in male C57BL/6J mice, which explored mountable objects longer than non-mountable ones and showed better discrimination between them (Heyser and Chemero, 2012). Climbing on an object can be considered as object exploration only when the head of the animal is directed towards the object, as a sign of paying attention on it. Neophobia towards objects, especially when encountering them for the first time, could be another potential factor affecting exploration of objects. Ennaceur and colleagues examined this possibility and found that rats did not exhibit neophobia towards objects (Ennaceur et al., 2009), while this issue is dependent upon the genetic backgrounds of rodents (Binder et al., 2015). A sufficient amount of object exploration time is also required to ensure that animals are not avoiding them. The biological rhythm may contribute to the level of exploration since rodents are nocturnal animals, and many studies have tested them during their “sleeping” time. Some studies on circadian phase have reported that when the NOP test was administered during rodents “sleeping time”, there was no influence on locomotor activity and object recognition (Beeler et al., 2006; Takahashi et al., 2013), but that OPP memory was affected, which has been shown to be better at night (Takahashi et al., 2013). Recent findings indicate that C57BL/6J mice kept under normal light/dark cycles perform better NOP memory at midday than midnight (Tam et al., 2017). Whereas sleep is important for memory consolidation (Binder et al., 2014; Born et al., 2006; Born and Wilhelm, 2012; Chen et al., 2014; Ishikawa et al., 2014; Prince et al., 2014), long-term NOP and OPP performance were impaired when sleep was interrupted after the learning trial (Sawangjit et al., 2018). Significant differences in memory processing may be expected in the comparison of normal versus reversed light-dark cycle. The light intensity applied during the test should not be over 350 lux, as evidenced by an impairment of NOP memory (Tam et al., 2016). To increase exploratory activity, rodents can be isolated in an empty cage for some minutes (Vanmierlo et al., 2016) or food-restricted for one week before the test (Wang et al., 2017a), although food restriction itself has been shown to have promnestic effects in adult and aged mice (Talhati et al., 2014). The definition of object exploration is variable between different laboratories. Some define object exploration as physical contact with objects, while others use exploration within a distance range, e.g. when animals approach an object within 2 cm. Compared to exploration without contact, the former criterion might underestimate the amount of exploration. The criterion for terminating the sample or test trial is also variable between studies and, thus, can influence the amount of exploration. Some apply a fixed time window of exploration,

e.g. 5 min per trial, while others use a fixed amount of object exploration, e.g. when animals explore objects for 20 seconds. The amount of time for exploring objects is usually taken as a measure of attention and/or motivation for object exploration. This measure can be obtained in data collected from experiments with a fixed duration (because there is variability in the amount of object exploration), but not from a fixed amount of exploration (because the amount of object exploration is equal for all subjects). Alternatively, animals could be excluded if the duration of object exploration is below a certain level, e.g. less than 10 seconds within 5 minutes. Overall, the level of exploration of objects is essential in NOP testing and the related factors need to be controlled.

If multiple sample trials are applied, the intervals between them influence object memory. For instance, application of five sample trials within one day resulted in weaker object memory than trials spaced over five consecutive days (Bello-Medina et al., 2013), which is consistent with previous studies (Anderson et al., 2008). This suggests that time plays an active role in regards to memory consolidation and this issue should be considered when several sample trials were applied.

NOP performance is variably dependent upon the time interval between the learning and test trials (Ennaceur and Delacour, 1988). Memory weakens over time unless it is strongly consolidated. Thus, the longer the retention interval, the more likely that retrieval/memory is disrupted. The time delay between trials of the NOP is a widely applied experimental factor for studying the extent of memory. Shorter versus longer retention intervals are taken as measures of short-term versus long-term memory (Kesner and Hunsaker, 2010). When a 0 second interval is applied in the NOP test, the performance could be taken as the measurement of “object-based attention” (Alkam et al., 2011; Alkam et al., 2013), and/or of ultra-short/working memory (Chao et al., 2018; Wang et al., 2017a). Early studies have indicated that rodents have memory for objects for up to 24 hours (Ennaceur and Delacour, 1988), and even up to 48 hours (Liu et al., 2016). With the help of sleep for the facilitation of NOP consolidation, the memory can be preserved for up to 3 weeks (Sawangjit et al., 2018). It is noted that the amount of object exploration in the learning trial is positively correlated with the degree of retention in regards to object exploration performance (at least within an amount of object exploration time). The longer the amount of object exploration, the more an animal remembers after a longer retention (Akkerman et al., 2012a; Federman et al., 2013; Ozawa et al., 2011). Therefore, the combination of different durations of object exploration and retention intervals can be used to create different strengths of memory. Discrepancies between studies can be due to the reason that one may apply a shorter object exploration during the sample trial to cause deficient memory after a shorter retention interval, while another might apply a longer object exploration time to establish intact memory after a longer delay. This factor is important in psychopharmacological studies, as researchers manipulate the extent of object memory to examine amnestic or promnestic effects according to the expected effect of the testing substance (Akkerman et al., 2014).

2.2. Object place preference (OPP)

A test similar to the NOP test has been adapted for assessing memory for an object situated in a particular place (Ennaceur et al., 1997). The same procedure as for the NOP test is

applied, except that one of the familiar objects is placed in a new location in the test trial to generate a setting for testing memory of *place* (Fig.1B). This design measures memory for where an object was located by testing for preference for a known object placed in a novel location. More exploration of the object at a new location than at its original location implies memory for the localization of the object in a previous location. OPP memory can be preserved longer than 1 week with the help of sleep (Sawangjit et al., 2018). In addition, it has been found that the half of the tested mice was able to retain OPP information for up to 6 months, but not after 1 year (Atucha et al., 2019).

The methodological factors which impact NOP also influence the OPP test. Spatial features around the testing arena are usually provided to serve as allocentric environmental cues. Thus, possible bias toward object-location could emerge due to spatial bias within the testing arena. This factor should be eliminated or controlled by adjusting the environment and/or counter-balancing the location of objects. In some earlier studies (Escorihuela et al., 1995; Howlett et al., 2004; Hryniewicz et al., 2007), one single object was presented, followed by the copy of the explored object and a novel object. In this case, the novelty pertains not only to the location of object, but also the identity of object (since the new object was novel in both place and identity). To control this factor, the new object can be placed at the previously old location, while the explored object is placed at a novel location (trying to counter-balance the “novelty”). As this design involves complex object and place interaction, the results should be carefully explained, and may likely not reflect only OPP processing. A variant of the OPP test used two distinct objects as the sample, while in the test trial two identical objects selected from either the explored type were placed at the familiar locations (Wilson et al., 2013c). This test is intended to measure the memory for the location of the changed object. However, since two distinct objects are used in the sample trial, it could simply reflect the mnemonic changes of local features (see 2.1.). Another OPP-like paradigm applies a single object during the learning trial, followed by two copies of the explored object, with one of them placed at the old location (Van Cauter et al., 2013). Since the identity of objects remains unchanged, the underlying processing should preferentially be engaged in dealing with *place*. The placing of animals into the testing arena from the same or different starting locations can potentially impact an OPP-like test, as it was shown that hippocampus-leisoned rats showed a memory impairment when starting to explore from different, but not the same, locations (see 3.3.2; (Langston and Wood, 2010).

2.3. Temporal-order preference

Spontaneous object exploration can be used to assess memory for *time* or for *temporal-order* memory (TOM). This test employs two sample trials and one test trial, separated by intervals (Mitchell and Laiacona, 1998). Sets of objects are presented in the two sample trials at distinct time points, and in the test trial one object from each set is placed together. A preference to explore more the object which was presented earlier than the one presented later, suggests a memory for differentiating how recently which object was encountered (Fig.1C).

The methodological factors in the NOP test are suggested to apply to the TOM test as well. Since there are two sample trials in the TOM test, the duration of exploration of objects on

both sample trials should be controlled. Otherwise, a bias toward one of the presented object sets could confound the outcome. Another notable factor is the time delay between the two sample trials, which presumably affects the memory strength between the two sets of objects. The TOM test is designed for animals to remember both sets of objects, while forming differential memory decay for each one. One could argue that the earlier presented object is explored more than the later one because of the forgetting of the earlier object. To exclude this argument, a separate NOP test can be used to investigate whether animals have memory for the object encountered in the first time point by applying an inter-interval interval corresponding to the summation of the two intervals applied in the TOM test. Studies have reported that rodents can retain object information for at least 24 hours after the exposure (Ennaceur and Delacour, 1988). Related information can be found in (Hatakeyama et al., 2018), who examined in detail the number of objects used in the sample trial, the exposure time for encoding and the length of the inter-trial interval using the TOM test.

An interesting question is whether animals can sence intervals of hours. Studies in training animals with classical and operant conditioning have shown that animals can behaviorally respond at certain intervals (seconds to minutes) according to the programmed stimulus (Kirsch et al., 2004; Kyd et al., 2008), which implies that animals can program intervals of seconds to minutes dependent on cognitive- and/or motivational-driven mechanisms. Long intervals of days can be timed with internal biological systems of circadian rhythms in animals (Buhusi and Meck, 2005). Timing intervals of hours in animals, however, is controversial. Rats are able to anticipate food with 24-, but not 18-hour intervals (Petersen et al., 2014), while 7–13 hour intervals were later found to be anticipated (Crystal, 2015). It was also reported that object information in the TOM test with interval of 3 (Barker et al., 2007), but not after 24 (Mitchell and Laiacona, 1998), hours could be “recognized” by rats.

2.4. Sense of time

In the sense of the common definition, “when” can be indicative of a specific time point, as well as a period of time (a time interval). Humans recollect an episode with both strategies. What about animals, do they retrieve an experience based only on how long ago? Episodic-like memory in animals might be qualitatively different compared to ours. Or does the essence of episodic-like memory in animals resemble human episodic memory in the ability to apply both strategies?

There are two critical studies addressing this issue. Using a similar paradigm as designed by Babb and Crystal (2006), Roberts et al. manipulated temporal cues of “when” (a specific time point during a day), “how long ago”, or both, to test rats’ episodic-like memory. They found that rats are sensitive to the cue of “how long ago”, but not to the cue of “when”, and questioned the similarity between episodic-like memory in animals and human episodic memory (Roberts et al., 2008). Zhou and Crystal (2009) conducted a study which dissociates the cue of “how long ago” with rewards and made rats retrieve an event according to “when”, *per se*. Their findings illustrated that rats are capable of recollecting episodic information according to the cue of a specific time point, which resembles human episodic memory (Zhou and Crystal, 2009). Another approach to study the *when* component of episodic memory in animals is to look into the future. Humans recollect a specific

experience in the past not only for remembering, but also for planning the future. The concept of "mental time travel" implies that the travel can be retrograde or anterograde. There is evidence that animals are capable of prospective memory defined as an ability to inactivate an action for a current situation but re-activate it again at an appropriate future time point (Wilson and Crystal, 2012; Wilson et al., 2013a).

The remarkable findings of time cells in the hippocampus has implications for the understanding of the neurobiology of time. The first clear evidence came from the hippocampal CA1 neuronal ensembles recorded during a task that required the rat to remember the order of a sequence of odor stimuli. Animals were trained to learn a series of odors presented one after another, and asked to recall the earlier odor in the test trial in which two previous odors selected from different time points were located together. The CA1 neuronal ensembles gradually changed across the learning trial, and the memory performance could be predicted by the strength of this neuronal pattern. Thus, the CA1 neurons encode the temporal context information during the mnemonic learning of the odor presentations (Manns et al., 2007). In head-fixed monkeys were asked to learn the order of two objects, presented one after the other with a time delay, and in the test trial required to indicate the correct sequence of the appearance of shown objects. Their hippocampal firing pattern altered along the passage of time during the delays (Naya and Suzuki, 2011). In an associative task rats were required to remember specific object-odor pairings, with an odor being presented 5 to 20 seconds after the presentation of an object. A profound finding was that some CA1 neurons responded specifically during the waiting period. In addition, these temporal context-relevant firing cells were changed when the delay was increased, irrespective of the locations or behaviors of the animals, and, thus, were termed "time cells" (MacDonald et al., 2011). Time cells were also identified in the CA3 region (Salz et al., 2016). The hippocampal neuronal firing patterns reflecting temporal context have also been shown to gradually change from seconds to minutes (Manns et al., 2007), hours to days (Mankin et al., 2012), and weeks (Rangel et al., 2014; Ziv et al., 2013). In contrast, the concept of *time* could just be a preconceived idea (e.g., influenced by Immanuel Kant) and the brain generates no such representation of time (and space), but instead, variations in the strength of neuronal communication simply guide the direction of neuronal activity flow underlying behaviors (Buzsáki, 2013; Buzsáki and Llinás, 2017). Nevertheless, the existence of "time cells" in the hippocampus provides the fundamental explanation of *when* in the neurobiology of memory (Eichenbaum, 2014, 2017a).

2.5. Spatial and non-spatial object preference (SNOP)

The spatial and non-spatial object preference (SNOP) test (Fig.1D) is a paradigm which applies four to five distinct objects for the assessment of object and location memories by changing the *place* and *identity* of objects sequentially (Lee et al., 2005; Save et al., 1992). The common version of this paradigm utilizes shorter inter-trial intervals, e.g., 3 min, which assesses spatial and object novelty or short-term memory (Hunsaker et al., 2007a; Lee et al., 2005; Vago and Kesner, 2008), while it can be adapted to longer intervals (Van Cauter et al., 2008a, b). For example, after the habituation to the testing arena, four to five distinct objects were presented and an animal was allowed to freely explore them for several sessions (encoding trials). Then, one of the objects was re-located to a novel place (spatial novelty

trial), followed by a novel object replacement (object novelty trial; Fig.1D). Rodents showed preference for exploring the displaced object more than the stationary ones, indicating intact spatial recognition. Also, they explored the novel object more than the familiar ones, as an indication for object recognition (Hunsaker et al., 2007a; Lee et al., 2005; Vago and Kesner, 2008).

Although the procedure of this paradigm is similar to the NOP and OPP tests, the differences between the SNOP and NOP/OPP tests are significant. First, the SNOP test applies more objects and more types of objects in the sample trial than the NOP/OPP tests, which involves complicated inter-object relationships (see section2.1. the discussion of applying distinct objects for learning). In this sense, the nature of this test is akin to the object-in-place test (see section 2.5) for measuring the memory for object/location-associative information. Second, the “quantity” of changed and unchanged information is not comparable between the SNOP test and NOP/OPP tests. For example, one out of five stationary objects is spatially changed in the SNOP test (1:4), compared to one of two stationary objects replaced in the OPP test (1:1). Third, the object novelty trial is followed by the spatial novelty trial, which could potentially be influenced by a sequential effect, e.g., the animal might be more alert in the object-novelty trial since it had learned that the object-contextual environment was altered in the spatial-novelty trial. Cautions should be applied in the interpretations of this paradigm.

Since the SNOP paradigm involves changing spatial and object information sequentially, the methodological factors in the NOP, OPP and TOM tests are also relevant for this test.

2.6. Object-in-place preference (OiP)

This paradigm was designed to evaluate recognition memory for the association of objects and their locations (Barker et al., 2007; Barker and Warburton, 2009, 2011b; Bussey et al., 2000; Good et al., 2007a). The OiP test involves one sample and one test trial, separated by a time delay. Four distinct objects, each at a different location, are presented in the sample trial, and two of them are interchanged by location in the test trial (Fig.1E). Rodents explored the two displaced objects more than the two that were stationary. This preference evidences that the animals have memory for the previous places of the objects, i.e., established an association between specific objects and specific locations (for review see (Warburton et al., 2013).

Compared to the NOP and OPP tests, the OiP test presents four distinct objects, instead of two identical objects, as the information to be learned. This test is similar to the SNOP test that applies multiple distinct objects in the sample trial and presumably requires higher memory capacity to learn than the NOP/OPP tests. In addition, since four distinct objects are presented, inter-object relationships are created which would likely engage somewhat different brain regions for memory establishment (see section 2.1.). Theoretically, a failure to form an OiP memory could result from deficits in either the NOP, the OPP, the association of object and location, or their combinations. Thus, the NOP and OPP tests are usually conducted independently along with the OiP test to exclude the factors for impairments in recognition of object or location (Barker et al., 2007; Barker and Warburton, 2011b, 2015; Barker and Warburton, 2018). Whereas the number of objects are fewer in the NOP/OPP

tests than in the OiP test (2 versus 4), another confounding possibility is that the OiP test may require higher memory load. If the OiP memory is disrupted, along with intact NOP and OPP performance, the compromised association of object and location might not be the sole reason.

The methodological factors in NOP and OPP tests are also applicable to the OiP test.

2.7. Episodic-like memory preference

The episodic-like memory test developed by Kart-Teke et al. (2006) is meant to gauge the integration of memory for NOP (*what*), OPP (*where*) and TOM (*when*) (Kart-Teke et al., 2006). The combined "what-where-when" memory, however, is not merely a summation of the three mnemonic components, given that "what-where-when" memory could be impaired under the circumstance of intact individual memory for "what", "where" and "when" (details see section 4.2). Thus, the development of such tests is essential for the understanding of the nature of the prototype of episodic memory. The Kart-Teke's paradigm is a training-free test in which two different sets of equal objects are used (Fig.2A). Four identical objects, the first set (sample trial 1), are placed at four of eight possible different locations at the periphery of the arena and animals are allowed to explore them for a period of time. The same procedure is applied after a time delay (inter-trial interval), with four objects from the second set (sample trial 2). Two of these four objects are placed at locations which were occupied by the previously presented objects (sample trial 1), while the other two objects are placed at locations which were not occupied before. After another delay, the test trial is applied with two objects from each set placed together: One object of each set is placed at the same location it occupied before, and the other is placed at a novel location. However, all the objects are placed only at locations that have been previously occupied in sample trial 1 or 2. Thus, a specific "what-where-when" setting is created, including one older familiar object at the stationary location (OS), one older familiar object at a displaced location (OD), one recent familiar object at the stationary location (RS) and one recent familiar object at a displaced location (RD) (called ELM2–2 test here: *the episodic-like memory test with the application of 2 sets of objects and displacement of 2 objects*). In this test, adult rats exhibit a pattern of exploration preferences, where RD > RS (*where*), OS > RS (*when*) and OS > OD. The exploration preference patterns, RD > RS (novel location over old one in recent familiar objects) and OS > OD (old location over novel one in older familiar objects), indicates an interaction between object-location and temporal-order, which demonstrates that the animals have episodic-like memory. Based on the duration of exploration of each object in the test trial, three indices are calculated:

$$\textit{Where}\ \text{index} = (\text{RD} - \text{RS})/(\text{RD} + \text{RS});$$

$$\textit{When}\ \text{index} = (\text{OS} - \text{RS})/(\text{OS} + \text{RS});$$

$$\textit{Interaction}\ \text{index} = (\text{OD} - \text{OS})/(\text{OD} + \text{OS}).$$

Positive values of the *where* and *when* indices represent the expression of memory for object location and temporal order. A negative value of the *Interaction* index is shown because of the exploration preference OS > OD exhibited by animals. This counterintuitive result (OS > OD) indicates that the exploration pattern of objects according to their location is influenced by the temporal-order in which they have been experienced in the past (Chao et al., 2016a; Chao et al., 2017; de Souza Silva et al., 2016; Drieskens et al., 2017) and provides a strong argument that the *what*, *where* and *when* information was not inter-communicating independently in this test. The reason for this OS > OD pattern might be due to weaker memory trace for *place* than for *time* of the first set of objects, whereby the higher exploration toward OS was proportionally contributed to by the interaction from the second set of objects (temporal order effect). Such an effect would not favor OD. This difference may come from the processing of the second sample trial in which half of the objects were located in previously occupied locations, while the other half was not. Thus, in the second sample trial, those objects at the new locations would form an active memory for place. In the testing trial, OD was placed at one of the locations related to an active *place* memory; whereas OS had always been located at the location with no such trace memory. The novelty for the displacement of OD could then be "nullified" by the previously active trace for place (reconsolidation effect). Thus, the animals explored OD like another RS. The uniqueness of this model is not only the measurement of *where* or *when* memory within a single test trial, but also the integration of distinct *what*, *where* and *when* properties being hypothetically converged into an "episodic-like memory". Therefore, a neurobiological system which integrates and organizes different sources of information to form such a memory should exist (as discussed below).

In another version of this paradigm the displacement of two objects is simplified to one object (called ELM2–1 test here; the recent familiar object at a displaced location, RD, is not presented; Fig.2B). In this case, object-location and temporal-order memory are tested, while the interaction between these two factors cannot be verified. In this test there is an exploration preference for the novel location over the old location of older-familiar objects (Dere et al., 2005a, b). Three indices can be derived from this paradigm:

$$\textit{Where}\ \text{index} = (\text{OD} - \text{OS})/(\text{OD} + \text{OS});$$

$$\textit{When}\ \text{index} = (\text{OS} - \text{averaged recent objects})/(\text{OS} + \text{averaged recent objects});$$

$$\textit{What}\ \text{index} = (\text{averaged older objects} - \text{averaged recent objects}) / (\text{averaged older objects} + \text{averaged recent objects}).$$

Positive values for these indices indicate intact memory for *where*, *when* and *what*.

The third version of episodic-like memory paradigm involves in four distinct objects (called ELM4–2 test here; Fig.2C). The principle concept of the ELM4–2 test (Barker et al., 2017; Davis et al., 2013a; Good et al., 2007a; Good et al., 2007b) is comparable to the Kart-Teke et al. paradigm (2006) by presenting OS, OD, RS and RD objects. However, the differences

between ELM4–2 and ELM2–2/2–1 are noted. First, the number of objects used in the sample trials is not identical (4 versus 2). Second, the types of objects are different, as four distinct objects versus two sets of identical objects, are used. This could increase the information complexity, as distinct inter-object relationships are formed in the *four distinct objects paradigm*. Third, the exploration pattern OD > OS is found, unlike that of the ELM2–2 test. These differences are due to the procedure for the applied number and types of objects in the sample and test trials. The comparison between the ELM4–2 and ELM2–2/ELM2–1 tests is similar to that of the NOP/OPP and SNOP/OiP tests (see sections 2.4 and 2.5). In this ELM4–2 paradigm, two indices can be calculated:

$$\textit{Where}\,\text{index} = [(\text{OD} + \text{RD}) - (\text{OS} + \text{RS})] / (\text{OS} + \text{OD} + \text{RS} + \text{RD});$$

$$\textit{When}\,\text{index} = [(\text{OS} + \text{OD}) - (\text{RS} + \text{RD})] / (\text{OS} + \text{OD} + \text{RS} + \text{RD}).$$

Positive values of *Where* and *When* indices demonstrate intact memory for object-location and temporal-order, respectively (Barker et al., 2017).

The original study using the ELM2–2 paradigm reported that the episodic-like memory was preserved for at least 1 hour (Kart-Teke et al., 2006). Studies manipulating the time interval between trials have shown that rats retain the episodic-like memory for over 2 hours (Belblidia et al., 2015), but not after 4–6 hours (Belblidia et al., 2015; Chao et al., 2014). Other studies have shown rats to retain “what-where-when” memory for up to 24 hours in the ELM2–1 test (Barbosa et al., 2010; Barbosa et al., 2013).

The replicability of the ELM2–2 and ELM2–1 tests is verified by independent laboratories (Barbosa et al., 2013; Castilla-Ortega et al., 2012; Castilla-Ortega et al., 2014; Drieskens et al., 2017; Fernandez and Garner, 2008; Inostroza et al., 2013a; Inostroza et al., 2013b; Lanté et al., 2015; Li and Chao, 2008; Lopez-Pigozzi et al., 2016; Wang et al., 2010). In addition, studies in neurodevelopment have taken the concepts and advantages of this model to bypass the expression of language to measure the “prototype of episodic memory” in toddlers and pre-school children (Bauer et al., 2016; Burns et al., 2015; Newcombe et al., 2014; Russell et al., 2011). Also, this model has been adapted for the assessment of episodic-like memory in adult humans for the investigations on age, sleep, emotion and clinical issues (Kinugawa et al., 2013; Mazurek et al., 2015; Pause et al., 2010; Weber et al., 2014; Zlomuzica et al., 2016). Findings and limitations of these tests are also well-reviewed by (Binder et al., 2015).

The episodic-like memory paradigms (Fig.2) are dependent upon the spontaneous object exploration tests of NOP, OPP and TOM, and thus, theoretically are influenced by all the methodological factors involved in these tests. Habituation to the environment, materials and properties of objects, configurations of placement of objects, spatial cues around the environment and time intervals between trials should be carefully controlled.

3. The prefrontal cortex, entorhinal cortex and hippocampus as a memory system

Based on studies of patients with injury to the medial temporal lobe, it is well-accepted that the hippocampus is crucial to the establishment of episodic memory (Burgess et al., 2002; Eichenbaum, 2013; Squire and Zola-Morgan, 1991; Tulving and Markowitsch, 1998). *In vivo* brain imaging studies during episodic encoding and retrieval have identified several other brain regions that are also critically engaged, including the PFC, retrosplenial cortex, parietal cortex and regions surrounding the hippocampus. The anatomical and functional interactions between these regions are intricate and implicated in the formation and retrieval of episodic memory. Diffusion tensor imaging and functional magnetic resonance imaging (fMRI) studies show strong links between the PFC and medial temporal lobe during episodic encoding (Schott et al., 2011; Schott et al., 2013). Electrophysiological recordings from epileptic patients during correct retrieval of episodic memory suggest the medial temporal lobe to act as a hub to interact with the lateral PFC and parietal cortex to form inter-regional connecting networks (Watrous et al., 2013). We will discuss the roles of the mPFC, EC and hippocampus in determining *what*, *where* and *when* object exploration tests and how their interaction influences the establishment of episodic-like memory.

Studies that do not focus on regional-specific effects, such as systemic or intracerebroventricular pharmacological administrations and global gene manipulations, will not be discussed here.

3.1. The role of the medial prefrontal cortex

Like in primates, the PFC in rodents is considered to participate in functions such as attention, decision making and memory (Chudasama, 2011; Dalley et al., 2004; Preston and Eichenbaum, 2013). The rodent mPFC can be anatomically divided into three subareas, namely the anterior cingulate cortex (ACC), prelimbic cortex (PLC) and infralimbic cortex (ILC), which are located along the dorsal – ventral axis (Dalley et al., 2004; Gabbott et al., 2005), and are reciprocally interconnected (Heidbreder and Groenewegen, 2003). Topographical distribution of projections are mapped from the dorsomedial PFC predominantly to sensorimotor regions and from ventromedial PFC to limbic regions (Hoover and Vertes, 2007). The mPFC could exert control over sensorimotor, emotional and memory systems through its glutamatergic axons (Hoover and Vertes, 2007). Projections of the prefrontal cortical γ-aminobutyric acid (GABA)-ergic neurons to the nucleus accumbens also exist (Lee et al., 2014). The mPFC has been discussed to be involved in planning, temporal processing, attention, behavioral flexibility, goal-directed, social and emotional behaviors (Dalley et al., 2004; Euston et al., 2012; Riga et al., 2014), and its interplay with the hippocampus is implicated in the processing of memory, especially episodic memory (Eichenbaum, 2017b).

The PFC neurons activate for storage of object information (Smith and Jonides, 1999), and ACC neuronal firing is correlated with exploratory behavior in the NOP test (Weible et al., 2009). Furthermore, *c-fos* (a marker for neuronal activity) expressing in the ACC was found when rats explored a novel object more than a familiar one (Zhu et al., 1995). However,

lesions in the mPFC did not affect NOP performance (Ennaceur et al., 1997; Mitchell and Laiacona, 1998), consistent with subsequent studies in rats and mice (Baran et al., 2010; Barker et al., 2007; Barker and Warburton, 2011b; Cross et al., 2012; McAllister et al., 2015; Spanswick and Dyck, 2012). Pharmacological inhibition of the mPFC with muscimol, a $GABA_A$-R agonist, also had no effect in the NOP test when infused before the sample trial (Neugebauer et al., 2018; Pezze et al., 2017). This implies that the mPFC is either not required for object recognition memory, or that other circuits compensate for this function when the mPFC is inactivated. Optogenetic stimulation of the mPFC glutamatergic neurons did not affect memory for NOP and OPP, but facilitated OiP memory, which is involved in object association information by switching inter-object locations (Benn et al., 2016). Whether the mPFC is engaged in memory for NOP, seems to depend on the properties of the object being encoded. When distinct objects were used as samples, object memory consolidation was deficient in animals with inactivated mPFC (Akirav and Maroun, 2006). A possible explanation is that associations between distinct objects (e.g. relative inter-object locations) are processed by the mPFC, while such associative learning is not required when identical objects are applied. This interpretation is in accordance with the perspective of the role of the PFC as a flexible supporter to memory when conditions demand “specificity” (Euston et al., 2012). Consistently, lesion of the mPFC disrupted memory in the OiP test in rats (Barker et al., 2007; Barker and Warburton, 2011b; Cross et al., 2012).

Alternatively, the mPFC has been suggested to play a specific role in memory consolidation and retrieval. A recent study showed that inhibition of the mPFC with Designer Receptors Exclusively Activated by Designer Drug (DREADD) given after the sample trial, impaired both NOP and OPP memories tested 24 and 4 hours later, respectively (Tuscher et al., 2018), suggesting a critical engagement of the mPFC in memory consolidation (Akirav and Maroun, 2006). Pre- (Nagai et al., 2007) or post-sample (Tanimizu et al., 2018) infusions of anisomycin, a protein synthesis inhibitor, into the mPFC disrupted long-term NOP memory in mice. Also, electrical stimulation of the ventromedial PFC facilitated NOP memory and hippocampus proliferation in middle-aged rats (Liu et al., 2015). In addition, pre-test microinfusions of muscimol into the rat ACC impaired the NOP memory tested after 24 hours, but not 20 min, implying the ACC is involved in the retrieval of NOP in a time-dependent manner (Pezze et al., 2017).

The prefrontal cortical neurons were found to respond to spatial goals (Hok et al., 2005) and single-cell recordings in the ACC demonstrated that the ACC is associated with OPP performance (Weible et al., 2009). In a modified NOP test in which only one of the explored objects was presented in the testing trial, some ACC neurons responded to the location of the absent object (Weible et al., 2012). When the PFC was damaged, however, the OPP memory was not influenced (Baran et al., 2010; Barker et al., 2007; Barker and Warburton, 2011b). Conversely, mice with PFC stroke showed impaired OPP, but not NOP, memory, along with reduced structural volume in the dorsal medial nucleus of the thalamus (Zhou et al., 2016). Long-term (24 hours), but not short-term (5 min), OPP memory was deficient when a cAMP response element binding protein (CREB)-binding protein, histone acetyltransferase, was reduced in the mouse PFC (Vieira and Korzus, 2015). Given that the mPFC and hippocampus interact in a complementary way to process spatial information (Chao et al., 2017; Eichenbaum, 2017b; Lee and Kesner, 2003; Maharjan et al., 2018), it is possible that

the object-place processing can be taken over by the hippocampus when the PFC is dysfunctional.

The PFC has been considered to account for the processing of *time*. TOM was impaired in rodents with selective lesions of the mPFC (Barker et al., 2007; Barker and Warburton, 2011b; Cross et al., 2012; Mitchell and Laiacona, 1998) or lidocaine injection (Hannesson et al., 2004). However, TOM deficits were not found in an animal model of ischemic lesion in the mPFC (Deziel et al., 2015). The catecholaminergic systems in the PFC are involved in the processing of TOM, given that catecholamine depletion in the mPFC induced by 6-hydroxydopamine (6-OHDA) disrupted this memory, but neither memory for NOP nor that for OPP (Nelson et al., 2011). However, this is contradicted by a similar study which reported impaired NOP memory after such a lesion (Kadowaki Horita et al., 2013). The findings in rodents are consistent with studies in human patients, with lesions to the ventromedial PFC, showing deficits in remembering past and imagining future events (Bertossi et al., 2016). The macaque ventrolateral PFC was also found to signal specific object-time relationships during a temporal order task (Naya et al., 2017).

The processing of OiP memory requires the participation of the mPFC, as evidenced by studies of lesions or blocking of glutamate-, acetylcholine (ACh)- or dopamine (DA)-R (Barker et al., 2007; Barker and Warburton, 2008, 2009, 2015; Savalli et al., 2015). In addition, medial prefrontal cortical DNA methylation, but not histone deacetylation, is involved in OiP memory (Scott et al., 2017). Thus, the medial prefrontal cortical DNA methylation, glutamate, ACh and DA systems mediate the recognition of specific object-place relationships.

The mPFC is unquestionably important for episodic-like memory. Higher expression of immediate early genes (*c-fos* and *zif-268*) was identified in the PFC and ACC after the learning of episodic-like memory employing conditioned-training of licking behavior (Veyrac et al., 2015). Higher *zif-268* expression was also found after exposure to the ELM2–2 test of episodic-like memory (Barbosa et al., 2013). Rats with mPFC damage exhibited defective “what-where-when” memory when tested by the contextual conditioning (Li et al., 2011). Mice with lesion of the mPFC showed the impaired *where*, but not *what* or *when,* component assessed in the ELM2–1 test (DeVito and Eichenbaum, 2010).

Neurotransmitter systems have profound impacts on multiple synaptic functions and behaviors. The diversity of neurotransmitters and their receptors (R) mediate a broad spectrum of physiological as well as pathological status.

3.1.1. Glutamate—Glutamate is the major excitatory neurotransmitter in the brain that activate ionotropic glutamate-R (e.g., AMPA-, kainate and NMDA-R) and metabotropic glutamate-R (e.g., mGluR). Intra-infusions of MPEP, a mGlu5-R antagonist, into the rat PLC disrupted spatial memory tested by a cross-maze and NOP memory test (Christoffersen et al., 2008). Infusion of 6-Cyano-7-nitroquinoxaline (CNQX), an AMPA/kainate-R antagonist, into the PLC/ILC region (the dorsal mPFC) had no effect when given before the learning trial of NOP (Barker and Warburton, 2011a). When CNQX was infused into the PLC/ILC, either before the second sample trial or before the test trial of the TOM test,

disrupted memory. Alternatively, intra-PLC/ILC infusion of 2-amino-5-phosphonopentanoic acid (AP5), an NMDA-R antagonist, impaired TOM performance when applied before the second sample trial, but not before the test trial (Barker and Warburton, 2011a). In the OiP test, pre-sample microinjections of CNQX or AP5 into the mPFC interfered short-term (5 minutes) memory in rats. The same pre-sample PFC infusions of AP5 also impaired OiP memory tested 1 hour later, but not when given pre-test (Barker and Warburton, 2008).

These findings indicate that the expression of NOP memory is dependent on the mGlu5-R, but not the AMPA/kainate-R, of the mPFC. The encoding/consolidation of TOM is dependent upon the medial prefrontal cortical AMPA/kainate- and NMDA-R, while AMPA/kainate-R, but not NMDA-R, are required for the retrieval of TOM. Both the PFC AMPA/kainate- and NMDA-R are indispensable for the encoding of specific object-location relationships, while NMDA-R engages in the learning and consolidation, but not recall, of OiP memory.

3.1.2. Dopamine—DAergic neurons in the brain largely originate from the substantia nigra pars compacta and ventral tegmental area, forming the nigrostriatal and mesocorticolimbic pathways, respectively. DA binds to a large family of G-protein coupled-R that can be classified into D1-like (D1- and D5-R; activate cyclic AMP production) and D2-like (D2-, D3 and D4-R; inhibit adenylyl cyclase activity). The interaction between the mPFC and midbrain DAergic systems plays a key role in the processing of NOP: A unilateral PFC lesion combined with a midbrain DAergic systems deficiency in the unilateral hemisphere, impaired NOP (90 min interval) if the lesions were in different hemispheres, but not when they were in the same hemisphere. The same disconnected lesions did not influence spatial working memory tested by a T-maze non-matching to place task (Chao et al., 2013). This implies that the midbrain DA interplays with the mPFC in the expression of NOP memory and that the communication between a non-lesioned side of the mPFC and midbrain DA systems is necessary for object memory. Interestingly, the rat with the unilateral DA deficiency also showed deficits in the TOM test, suggestive of a relationship between “time”, DA systems and PFC/hippocampus functions (Chao et al., 2013). Transcranial direct current stimulation onto the PFC also increased DA levels in the hippocampus and striatum, and NOP memory was thereby improved in spontaneous hypertensive rats (Leffa et al., 2016). In addition, DA levels were found to be elevated in the mPFC during the test trial of NOP memory in rats (McLean et al., 2017).

When administrated prior to the sample trial, microinjections into the mPFC of the DA D1/5-R agonist SKF81297 facilitated, and its antagonist SCH23390 disrupted, NOP memory tested 24 hours later (De Bundel et al., 2013; Nagai et al., 2007). Microinjections of SCH23390 into the PFC, but not into the hippocampus, also blocked the facilitating effects of systemic reboxetine, a norepinephrine (NE) reuptake inhibitor, on the performance of long-term NOP (De Bundel et al., 2013). Pre-sample prefrontal microinjections of SCH23390 did not impair the NOP memory tested 1 hour later (Savalli et al., 2015), although contrary results have also been reported (Clausen et al., 2011). Pre-sample infusions of SKF81297 into the PFC impaired short-term (1 hour) NOP (Pezze et al., 2015). In the OiP test, pre-sample infusions of SCH23390 or SKF83566, a DA D1-R antagonist, into the rat mPFC led to an impairment, tested 5 and 1 hour later. Pre-test infusions of

SCH23390 into the PFC had no effect in the OiP (1 hour) memory (Savalli et al., 2015). The D1/5-R of the mPFC could bidirectionally regulate the encoding and/or consolidation of NOP memory, probably compatible with their inverted U-shape functions in the processing of working memory (Cools and D'Esposito, 2011). Together, the prefrontal cortical D1-R underlie the learning and/or consolidation, but not retrieval, of object-location relevant information.

Pre-sample microinjections of the DA D2-R antagonist L-741.626 into the PFC dose-dependently disrupted short-term NOP (2 min interval), which is consistent with its effects with acute systemic administration (Watson et al., 2012). Pre-sample infusions of the D3-R antagonist S33084 into the rat PFC dose-dependently improved NOP (4 hours interval), supported by the findings when injected systemically (Watson et al., 2012). Thus, pharmacological blockage of the prefrontal cortical DA D2- and D3-R leads to NOP deficiency and facilitation, respectively.

Microinjections of the D1-R antagonist SCH23390, the D2-R antagonist L-741.626 or the D3-R agonist 7-OH-DPAT into the PFC after the sample trial dose-dependently impaired NOP memory when tested 1 hour later (Papp et al., 2017). Conversely, post-sample microinjections of the D1-R agonist SKF81297, the D2-R agonist quinpirole or the D3-R antagonist SB277,011 into the PFC facilitated NOP memory when tested after 24 hours (Papp et al., 2017). However, a study shows that post-sample PFC infusions of quinpirole did not affect NOP performance (Rossato et al., 2013). Infusions of SCH23390 into the PFC also impaired long-term 24 hours NOP memory when administrated immediately, but not 6 hours, after the sample trial (Rossato et al., 2013). These results suggest that the prefrontal cortical DA D1-, D2- and D3-R critically modulate the NOP consolidation. Pharmacological blockage of DA D1- and D2-R and activation of D3-R disrupt short-term object consolidation, but pharmacological activation of DA D1- and D2-R and blockage of D3-R facilitate long-term object consolidation.

Collectively, DA plays a significant role in the regulation of the prefrontal cortical functions in the encoding and consolidation of NOP and OiP processing, irrespective of short- or long-term memory.

3.1.3. Serotonin—The primary source of serotonin (5-HT) derives from the raphe nuclei that project to the central nervous systems. 5-HT, by executing its action through the binding to more than 14 types of 5-HT-R, have received emphasis in the modulation of PFC-related functions and memory processing (Meneses, 2015). For instance, the selective 5-HT reuptake inhibitor escitaplopram, but not citaplopram, facilitated the NOP memory, increased the neuronal firing rate of ventral tegmental area *in vivo*, and potentiated the mPFC NMDA-R mediated currents *in vitro* (Schilstrom et al., 2011).

Pre-test microinjections of MDL 11,939, a 5-HT2A-R antagonist, into the rat mPFC impaired TOM, but not NOP and OPP, all with 3 hours intervals (Bekinschtein et al., 2013). In the object-in-context (OIC) test, different sets of objects are presented at distinct contexts and animals are later asked to recognize which object is incongruent to the testing context. Pre-test prefrontal infusions of MDL 11,939 or 8-OH DPAT, a 5HT1A-R agonist, but not of

SB 242084, a 5HT2C-R antagonist, also impaired OIC memory tested 3 hours later (Bekinschtein et al., 2013). These findings suggest that 5HT2A-R in the mPFC are critical for memory retrieval in short-term TOM, but not for NOP and OPP. The prefrontal 5HT1A-R and 2A-R, but not 2C-R, are also important in the retrieval of short-term OIC memory.

3.1.4. Acetylcholine—ACh, binding to the two main nicotinic and muscarinic ACh-R, is profoundly involved in cognition and memory processing (Hasselmo and Sarter, 2011). The medial septum and vertical diagonal band of Broca (MSvDB) send projections to the hippocampus to form the septo-hippocampal cholinergic pathways. The baso-cortical cholinergic pathways from the nucleus basalis magnocellularis (NBM) project to the entire cortex (Mesulam et al., 1983).

Infusion of the muscarinic ACh-R antagonist scopolamine into the PLC/ILC before the second sample trial, but not before the test trial, of the TOM test disrupted memory (Barker and Warburton, 2011a). Similarly, pre-sample, but not pre-test, microinjections of scopolamine into the mPFC caused deficient OiP memory tested 5 minutes and 1 hour later (Barker and Warburton, 2009). When OiP memory was tested 24 hours later, pre-sample, but not pre-test, PFC infusions of the α7 nicotinic ACh-R antagonist, methyllycaconitine citrate, or the α-nicotinic ACh-R blocker, α-bungarotoxin, impaired memory. Conversely, microinjections of the α4β2 nicotinic ACh-R antagonist, dihydro-β-erythroidine hydrobromide, into the PFC led to deficient OiP memory when given pre-test, but not pre-sample. Post-sample PFC infusions of neither methyllycaconitine citrate nor dihydro-β-erythroidine hydrobromide influenced OiP memory. In addition, infusions into the mPFC of methyllycaconitine citrate, before learning, or dihydro-β-erythroidine hydrobromide, before the test trial, did not influence OPP (24 hours) memory (Sabec et al., 2018).

The muscarinic ACh-R of the PLC/ILC are essential for the encoding/consolidation, but not retrieval, of TOM and OiP. The medial prefrontal cortical α7 nicotinic ACh-R underly the learning, but not consolidation and recall, of associative object-location memory, while the α4β2 nicotinic ACh-R are responsible for the retrieval, but not learning and consolidation, of this memory. Neither α7- nor α4β2-nicotinic ACh-R seem to be significantly involved in OPP memory. These findings suggest that the muscarinic and nicotinic ACh-R in the mPFC have different roles in processing the information of time and associative object-location.

3.1.5. Short summary—Lesion and inactivation studies have provided substantial evidence that TOM, OiP and episodic-like, but not NOP and OPP, memories are dependent on the mPFC. However, the mPFC may mediate memory consolidation, regardless of types of object exploration tests. Furthermore, pharmacological studies have found that NOP memory tested even minutes later was impaired by pre-sample infusions of substances into the PFC (Christoffersen et al., 2008; Pezze et al., 2015; Watson et al., 2012). Details of findings of substances injected locally into the mPFC are listed in Table 1. The results suggest that it may not be the mPFC is irrelevant to NOP processing, but rather other neural systems take over when the mPFC is dysfunctional.

3.2. The role of the entorhinal cortex

Evidence has shown that the EC is involved in spatial recognition and long-term memory. EC-lesioned animals showed deficient spatial navigation in the Morris water maze (Nyakas et al., 2009; Parron et al., 2004), but not when spatial cues were provided by proximal objects located in the pool (Parron et al., 2004). The EC-lesioned rats have also been reported to show deficits in the NOP test with an 2-hour interval (Nyakas et al., 2009). Post-sample intra-EC infusions of the protein synthesis inhibitors, anisomycin, emetine or cycloheximide, disrupted long-term (24 hours), but not short-term (3 hours), NOP memory. This disruption was time-dependent as the effect was found when infusions were made immediately, but not 3 or 6 hours, after the sample (Lima et al., 2009). Thus, the EC participates in long-term memory consolidation of object memory. In the SNOP test, impaired spatial recognition and less object exploration were found in EC-lesioned animals (Parron and Save, 2004). The EC lesioned animals also exhibited deficits in habituation to the environment when the time delay was 10, but not 4 min. In addition, impaired spatial recognition, but not object recognition, was found, irrespective of the delays (Van Cauter et al., 2008a). This indicates that the EC is important for maintaining spatial information across time in memory storage. Furthermore, electrical stimulation of EC facilitated NOP memory and water maze spatial navigation in rats infused with the amyloid peptides 1–42 into the hippocampus, as a model of Alzheimer's disease (Zhang et al., 2015), suggestive of close connections between the EC and hippocampus-dependent functions.

The EC, located in the medial temporal lobe, can be anatomically subdivided into lateral and medial compartments. The LEC preferentially receives projections from the perirhinal cortex, insular cortex, PLC and ILC, while the medial entorhinal cortex (MEC) mainly connects with the postrhinal, occipital and parietal cortical regions in rats (Burwell and Amaral, 1998a, b; Witter et al., 2000). Projections from the perirhinal cortex to LEC and those from the postrhinal cortex to MEC are functionally different, with the former primarily sending inhibitory signals (Apergis-Schoute et al., 2007; Pinto et al., 2006; Willems et al., 2018) and the latter primarily sending excitatory ones (Koganezawa et al., 2015). The dominant projections of the perirhinal-LEC and postrhinal-MEC pathways have inspired scientists to propose a neuroanatomy system of episodic memory that integrates spatial representation from the postrhinal-MEC pathway and non-spatial representation from the perirhinal-LEC pathway into the hippocampus (Davachi, 2006; Deshmukh and Knierim, 2011; Eichenbaum et al., 2007; Hargreaves et al., 2005; Knierim et al., 2006; Schultz et al., 2012). Yet, recent behavioral and electrophysiological evidence indicates that both LEC and MEC process spatial information, with local and global spatial frameworks being represented within LEC and MEC, respectively (Knierim et al., 2014; Neunuebel et al., 2013).

In non-spatial (*what*) object exploration tests, lesions of the LEC of rats spared memory in the classic NOP test (Kuruvilla and Ainge, 2017; Van Cauter et al., 2013; Wilson et al., 2013b; Wilson et al., 2013c), but impaired object memory when 3 or 4 distinct objects were used during the learning (Hunsaker et al., 2013; Kuruvilla and Ainge, 2017). This finding is in agreement with others, indicating the LEC is critical for the memory of associations between different objects, even contexts (Hunsaker et al., 2013; Kuruvilla and Ainge, 2017;

Wilson et al., 2013b; Wilson et al., 2013c). Evidence from the SNOP test has supported this perspective, as object recognition was compromised when four distinct, but not identical, objects were required to be remembered by LEC lesioned rats (Rodo et al., 2017; Van Cauter et al., 2013). When reducing the diversity of objects to three distinct objects, the LEC-lesioned animals were able to show intact object recognition in the SNOP test (Rodo et al., 2017). These results indicate that the LEC processes complicated, but not simple, inter-relationships between objects. Compatible with this view are the imaging findings that the LEC was more recruited in the processing of the number of items (5 versus 10 odors) during the recall of a non-matching to sample task (Ku et al., 2017). In contrast, MEC lesions affected neither the NOP test (Hales et al., 2014; Hales et al., 2018; Hunsaker et al., 2013; Kuruvilla and Ainge, 2017; Van Cauter et al., 2013) nor object novelty as assessed by the SNOP test (Rodo et al., 2017; Van Cauter et al., 2013). Pre-test microinjections of scopolamine into the MEC also had no effect in the NOP test, but decreased the amount of object exploration (Rashid and Ahmed, 2019). Thus, the LEC, but not MEC, critically processes object-object inter-relationships when environmental complexity (object associative information) increases.

In an OPP-like paradigm to test spatial (*where*) object exploration, in which a single object was presented in the sample trial and another identical object was placed together with the familiar one in the test trial, memory was disrupted in animals with lesion of the MEC, but not LEC (Van Cauter et al., 2013). However, another study showed that lesions of the MEC did not disrupt memory in the OPP test, but impaired spatial memory tested by the water maze escape task and that combined lesions of the MEC and hippocampus led to a stronger impairment (Hales et al., 2014). In the SNOP test, impaired spatial recognition was found after lesion of the MEC (Rodo et al., 2017; Van Cauter et al., 2013). The MEC-lesioned animals exhibited deficits in spatial recognition when three or four distinct, but not identical, objects were used in the sample trial of the SNOP test (Rodo et al., 2017). These data illustrate the engagement of the MEC in the processing of “general” information about space and its interaction with the hippocampus (Hales et al., 2014; Hales et al., 2018), particularly in situation with increased complexity of objects. It should be noted that lesions of the MEC may mask its specific role in the processing of spatial information. For example, inactivation of the superficial layers of MEC stellate cells impaired memory for OPP, but not NOP, in mice (Tennant et al., 2018). Lesions of the LEC, on the other hand, did not affect OPP memory (Van Cauter et al., 2013; Wilson et al., 2013c), but impaired object-location recognition in a test in which two distinct objects were replaced by two identical ones, chosen from either of the explored type (Wilson et al., 2013c). Impaired spatial recognition was also reported in the LEC-lesioned rats tested by the SNOP paradigm (Van Cauter et al., 2013), but see (Rodo et al., 2017). In the same vein, the LEC-lesioned rats showed deficits in searching for foods in an arena in which spatial cues were provided by two distinct objects located within the environment (Kuruvilla and Ainge, 2017). Space-relevant object recognition can be mediated by both LEC and MEC, depending on the diversity of objects explored.

A summary of the roles of LEC and MEC in the object exploration tests is shown in Table 2 and Figure 3. Please note that less object exploration and habituation to the testing environment were sometimes reported in the mentioned studies (Parron and Save, 2004; Van

Cauter et al., 2013; Van Cauter et al., 2008a), which could potentially confound the observed performance. Secondly, the majority of lesion studies has applied less than 10-minutes retention intervals (consequences are not clear after longer delays). The whole EC is likely to engage in long-term object memory, given that EC-lesioned or inactivated animals exhibited deficits in the NOP test when tested 24 hours later (Lima et al., 2009; Nyakas et al., 2009). How the LEC and MEC contribute to long-term memory in regards to spatial and non-spatial processing remains unclear.

Behavioral, imaging and electrophysiological recording data suggest that LEC preferentially processes object-associated information, e.g., the past and current locations of objects (Beer et al., 2013; Deshmukh and Knierim, 2011; Tsao et al., 2013; Van Cauter et al., 2013), and the context of the objects (Wilson et al., 2013b; Wilson et al., 2013c). Intriguingly, populations of LEC neurons also encode temporal information across different contexts (Tsao et al., 2018). This matches the anatomical features of LEC, as being a functional hub for integrating multisensory information (Bota et al., 2015), including both spatial and non-spatial characteristics, probably even *time* (Tsao et al., 2018). In contrast, the MEC neurons fire for location in the environment and across different contexts, forming “grid-like” activities (Fyhn et al., 2004; Hafting et al., 2005). Strikingly, the MEC neurons respond at fixed distances and directions from objects, irrespective of location, shape and size of objects, and have been called *object-vector* cells (Hoydal et al., 2019). Anatomical, electrophysiological and behavioral evidence suggests that the LEC and MEC have some convergent functions: a). The perirhinal cortex and postrhinal cortex project to the MEC and LEC, respectively, although in lesser extent than the perirhinal-LEC and postrhinal-MEC connections (van Strien et al., 2009), and there are reciprocal interconnections between the LEC and MEC (Burwell, 2000; Dolorfo and Amaral, 1998), which provide an anatomical basis for the involvement of the mixture processing of “spatial” and “non-spatial” information in both entorhinal compartments, b), the LEC and MEC neurons signal both information about objects and position (Keene et al., 2016), and c), the MEC lesioned rats had deficits in the recollection of an odor-based, non-spatial, recognition task, suggesting a broader role of MEC in memory function (Sauvage et al., 2010). Save and Sargolini thus proposed that the roles of LEC and MEC in non-spatial and spatial processing are environmental complexity-dependent (Rodo et al., 2017), whereby they integrate *what* and *where* information into the hippocampus in a tightly cooperative and flexible manner (Save and Sargolini, 2017).

3.3. The role of the hippocampus

3.3.1. Novel object preference—The role of the hippocampus in the processing of NOP is contentious. The hippocampus is not required for short-term NOP memory (less than 10 minutes) shown by lesion and inactivation studies (organized in Table 3). Inconsistent findings were reported in the literature when the retention delay was over 10 minutes in the NOP test. Some studies showed that rats with hippocampal lesions had impaired NOP (across delays from 10 minutes to 24 hours) memory (Ainge et al., 2006; Broadbent et al., 2010; Broadbent et al., 2004; Clark et al., 2000), whereas the majority of the studies employing hippocampal lesions in rats failed to report an influence in the NOP test (Albasser et al., 2012; Albasser et al., 2010; Barker and Warburton, 2011b; Forwood et al.,

2005; Gaskin et al., 2003; Good et al., 2007a; Langston and Wood, 2010; Mumby et al., 2005; Piterkin et al., 2008; Tam et al., 2014; Winters et al., 2004). Alternatively, pre-sample intra-hippocampus infusions of lidocaine (Hammond et al., 2004) or muscimol (Cohen et al., 2013) was reported to disrupt NOP memory tested 24 hours later in mice. Similar effects were also found in a circular track in which animals explored newly and repeatedly presented objects in a clockwise order (Bass et al., 2014).

On the other hand, the hippocampus is likely involved in NOP consolidation and/or retrieval. Hippocampal CA1 firing rates were enhanced during NOP testing (Cohen et al., 2013) and NOP consolidation is related to an increase of the hippocampal CA3-CA1 synaptic efficacy (Clarke et al., 2010). Both CA1 and CA3 areas (more CA1 than CA3) were recruited in the NOP test (Beer et al., 2013). In studies investigating retrograde memory, animals with hippocampus lesion, after being submitted to repeated exposure of the sample trial in the NOP test, exhibited impaired recognition memory when tested within 5, but not 8, weeks after the lesions (Broadbent et al., 2010; Gaskin et al., 2003; Haijima and Ichitani, 2012). Thus, an intact learning is not sufficient to support the memory if the hippocampus was damaged afterward. Post-sample intra-hippocampus infusion of muscimol impaired long-term NOP (24 hours) memory (Cohen et al., 2013; Haettig et al., 2011), but see (Oliveira et al., 2010). Interestingly, post-sample infusions of muscimol and the GABAa-R antagonist bicuculline into the dorsal hippocampus respectively facilitated and disrupted long-term NOP memory in a less-habituated environment, but not after sufficient habituation (Kim et al., 2014; Oliveira et al., 2010). This suggests that the dorsal hippocampal GABAa-R dually modulate NOP consolidation when contextual information is relatively novel. The ventral hippocampus is also involved in NOP memory, as muscimol infusions led to NOP deficits (Neugebauer et al., 2018), albeit this was not supported by a lesion study (Broadbent et al., 2004). Post-sample infusions of anisomycin into the hippocampal CA1 area impaired long-term (24 hours), but not short-term (3 hours), NOP memory when it was infused within 3, but not 6, hours after the sample trial (Rossato et al., 2007), whereas no effect was reported (Balderas et al., 2008). Similar results were found with intra-CA1 infusion of anisomycin, which impaired NOP consolidation and reconsolidation, and the reconsolidation effects of which were reversed by the ubiquitin-proteasome system inhibitor β-Lactacystin (Furini et al., 2015). Post-sample intra-CA1 infusions of lactacystin also disrupted long-term NOP memory, but in a time-dependent manner (Figueiredo et al., 2015). A recent study showed that chemogenetic inhibition (KORD), but not hM4Di, of the dorsal hippocampus impaired NOP consolidation tested 24 hours later (Tuscher et al., 2018). Pre-test muscimol microinjections into the dorsal hippocampus was reported to impair (Cohen et al., 2013; Stackman et al., 2016) or not affect (Haettig et al., 2011) NOP memory in mice.

It has also been shown that the hippocampal neurogenesis is important for the existed object information (Suarez-Pereira and Carrion, 2015). The hippocampal dentate gyrus is involved in NOP processing as evidenced by destruction of high K+ infusions into the region leading to NOP deficits, either treated before or after the sample trial (Suzuki et al., 2015). NOP memory also elevated the AMPA/NMDA current ratio in the dentate gyrus (Yang et al., 2017). However, lesions in the dorsal dentate gyrus did not induce NOP/OPP deficits in rats (Beselia et al., 2010), and DREADD activation of GABAergic parvalbumin neurons in the dentate gyrus also showed no effect in the NOP test, but influenced anxiety-like behaviors,

social novelty and contextual fear extinction in mice (Zou et al., 2016). Whether the dente gyrus engaging in object memory depends on situations when configurations of object-feature or -context were altered (Dees and Kesner, 2013; Kesner et al., 2016; Kesner et al., 2015).

The hippocampus actively processes contextual cues. Rats with hippocampus lesions exhibited intact NOP tested in the same environment, but not in different one. However, opposite results were found if only local cues proximal to the applied objects were altered: The control animals had deficient NOP memory in the changed context, but intact memory in the same one, while the lesioned animals remembered the objects in both cases (Piterkin et al., 2008). This is consistent with a later study in which pre-test microinjection of muscimol into the dorsal hippocampus impaired NOP memory when encoded and recalled in different environments (Cohen et al., 2013). Thus, the hippocampus processes the information about located objects within a specific context.

Taken together, the hippocampus is not essential for NOP memory when the retention is less than 10 minutes. The hippocampus engagement in the processing of NOP memory over 10 minutes depends on many factors. Lesion extent of the hippocampus has been discussed, in that severe, but not partial, lesions influenced NOP memory (Broadbent et al., 2004). Yet, the effects of severe hippocampal lesions could be confounded by less object exploration during the NOP encoding (Ainge et al., 2006). Lesions of the hippocampus also influenced memory load, i.e., how many types and numbers of objects can be remembered. Studies have shown that the dorsal hippocampus-lesioned mice were impaired in remembering six distinct objects (Sannino et al., 2012), although this finding seems hard to explain the mentioned discrepancies because two identical objects are usually used in the NOP test (Table 3). Method of lesion (e.g., permanent versus transient lesions) can be a factor; in the majority of studies the non-effect of hippocampus lesions is likely to reflect a functional compensation, such as the reorganization of neuronal circuits in hippocampus-associated regions (Cohen and Stackman, 2015). However, a non-effect of pharmacological inactivation on the dorsal hippocampus was reported in the NOP test if animals were well-habituated to the testing environment (Kim et al., 2014; Oliveira et al., 2010). The majority of chemogenetic studies, either activated before or after the sample trial, showed no influence in the 24 hours-delayed NOP test by overall excitation or inhibition on the dorsal hippocampus, or selectively on the excitatory glutamatergic neurons or inhibitory interneurons in the region (Lopez et al., 2016; Tuscher et al., 2018; Yu et al., 2018; Zou et al., 2016). Nevertheless, long-term NOP impairment was consistently found when the hippocampus was damaged after the learning session (Broadbent et al., 2010; Gaskin et al., 2003; Haijima and Ichitani, 2012). Thus, the hippocampus is undoubtedly important for NOP memory when the retention is over 10 minutes (Cohen and Stackman, 2015), while its involvement likely depends on contextual novelty (Kim et al., 2014; Oliveira et al., 2010; Yi et al., 2016), features of context (Piterkin et al., 2008), and probably allocentric signals (Langston and Wood, 2010) (see below).

3.3.2. Object place preference—The OPP test has been shown to be hippocampus-dependent in rodents (Barker and Warburton, 2011b; Mumby et al., 2002). This is compatible with the classical consensus that the hippocampus is a critical brain region for

processing spatial information. Electrophysiological recordings of the hippocampal CA1 cells have shown that when the location of two objects was rotated, the CA1 firing pattern remapped, suggesting that the CA1 coordinated the altered spatial information (Lenck-Santini et al., 2005). CA1 firing rate was also increased during the OPP test, especially when a novel object was placed at a new location (Larkin et al., 2014). CA1 and CA3 pyramidal neurons were reported to code object information in location when the objects were spatially displaced (Deshmukh and Knierim, 2013; Manns and Eichenbaum, 2009). CA1 area was required in both object and location conditions, while CA3 was more recruited for OPP than NOP (Beer et al., 2013). Likewise, the CA1 neuronal firing pattern was reorganized during the learning of searching for a new goal in a spatial memory task (Dupret et al., 2010). Higher *c-fos* expression induced by the OPP, but not NOP, test was found in the hippocampal CA1 and CA3 subregions (Mendez et al., 2015), while *Arc* mRNA imaging data showed higher involvement of CA3 in OPP than NOP (Beer et al., 2013). OPP memory also increased the expression of other immediate early genes, such as *Arc*, *Zif268* and *Narp*, and enhanced the protein levels of Arc, postsynaptic density protein 95 (PSD-95) and αCaMKII in the hippocampal dentate gyrus (Soule et al., 2008). In addition, the newborn cells of dentate gyrus are critical for OPP memory (Jessberger et al., 2009). A study has reported that hippocampal lesioned rats showed intact memory when tested by a paradigm similar to OPP with a 2 min interval. Interestingly, in this OPP-like test in which two distinct objects were presented and only one of their kind was presented later, the rats with hippocampus lesions exhibited disrupted memory when placed into the testing arena from different starting locations, but not from the same location (Langston and Wood, 2010). This suggests that the hippocampus encodes allocentric information of located objects, which is compatible with the findings of the *landmark-vector* properties of CA1 pyramidal neurons (Deshmukh and Knierim, 2013). The dorsal, but not ventral, hippocampus has been shown to be critically involved in OPP memory (Gaskin et al., 2009a), leading to disrupted OPP memory tested 2 hours, but not 5 min, later (Tam et al., 2014). The functional separation of dorsal versus ventral hippocampus in the processing of memory could be associated with the dominant role of the dorsal hippocampus in both, encoding and retrieval processes (Nakamura and Sauvage, 2016).

Pre-sample lidocaine infusion into the CA1 subarea of the dorsal hippocampus disrupted OPP memory in mice (Assini et al., 2009). Post-sample trial muscimol or anisomycin microinjection into the hippocampus also impaired long-term OPP memory (Oliveira et al., 2010; Ozawa et al., 2017). Furthermore, when injected 3 hours, but not 5 days, after the sample trial, intra-hippocampal infusions of muscimol injected twice daily for 4 consecutive days, impaired long-term OPP memory which was tested 2–4 days after the last infusion of muscimol (Gaskin et al., 2011). This finding is consistent with the previous lesion study in which OPP memory was spared in hippocampus-damaged animals, if the lesion was made 3 weeks, but not 1–3 days, after the learning trial (Gaskin et al., 2009b). Pre-sample, but not pre-test (Ozawa et al., 2017), infusions of anisomycin into the dorsal hippocampus impaired long-term OPP memory in the rat (Moncada, 2017; Ozawa et al., 2014, 2017). Similar effects were found with pre-sample infusions of the protein synthesis inhibitor emetine and the mRNA synthesis inhibitor 5,6-dichlorobenzimidazole 1-β-D-ribofuranoside into the dorsal hippocampus, while these infusions did not influence short-term (5 min) OPP

memory (Ozawa et al., 2017). This suggests that learning and/or consolidation of long-term OPP is dependent on protein and mRNA synthesis in the hippocampus. Pre-test intra-hippocampus infusions of muscimol also disrupted OPP memory tested 24 hours later in rats (Gaskin et al., 2011), supporting a critical role of the hippocampus in the retrieval of long-term OPP memory.

Mice with specific inactivation of the hippocampal excitatory or inhibitory neurons exhibited long-term OPP deficits, suggesting that both excitatory and inhibitory neurons are cardinal for this memory (Haettig et al., 2013). In line with these findings, application of DREADDs by transferring excitatory- (M3Dq)- or inhibitory- (M4Di)-R into the dorsal hippocampus, led to improved long-term memory for OPP, but not NOP, in the M3Dq-activated mice, while the M4Di-activated animals showed the opposite (Lopez et al., 2016). Deficits in OPP memory (4-hour inter-trial interval) were also found when the dorsal hippocampus was, either pre- or post-sample, chemogenetic inhibited (M4Di or KORD) in the ovariectomized female mice (Tuscher et al., 2018). Post-sample activation of M3Dq selectively in the CA1 interneurons also impaired long-term OPP, but not NOP, memory in mice (Yu et al., 2018). In a simultaneous assessment of mnemonic information processing for NOP versus OPP, rats with lesioned hippocampus showed the preference for novel object over novel location (Chao et al., 2016b). This result implies that information about object, but not location, can be functionally compensated when the hippocampus is damaged. Overall, it is clear that the hippocampus plays an important role in OPP memory, which can be mediated by the hippocampal excitatory and inhibitory neurons.

Distinct hippocampal subregions are activated by different object stimuli that combine “what” and “where” components. For instance, in a setting of exploring three small “positionally” distinct objects, the distal CA1 and proximal CA3, which preferentially receive “what” information (Mishkin et al., 1983), were recruited during the recognition of a novel object (increased mRNA of the immediate early genes *Arc* and *Homer1a*), whereas the proximal CA3 and lower blade of dentate gyrus, but not CA1, were involved in novel object recognition during exploring three large “directionally” distinct objects (Hoang et al., 2018). The neuronal plasticity of hippocampal long-term potentiation (LTP) and long-term depression (LTD) underlie object exploration processes. When encountering a novel environment, LTP was enhanced in the CA1, dentate gyrus and CA3 (Hagena and Manahan-Vaughan, 2011; Kemp and Manahan-Vaughan, 2008), suggesting that the cellular mechanism is common for such a situation. In the NOP test, LTD was facilitated in the CA1 (Goh and Manahan-Vaughan, 2013c). During “positional” object exploration, LTD was enhanced in the CA1 region, but not dentate gyrus, while the opposite results were found during “directional” object exploration (Kemp and Manahan-Vaughan, 2008). Interestingly, LTD was facilitated at the commissural-associational fibers in CA3 during the “positional” object exploration test, but not at the mossy fibers from the dentate gyrus projecting to the CA3. In the “directional” object exploration setting, the mossy fibers-CA3 LTD was facilitated, but not the commissural-CA3 LTD (Hagena and Manahan-Vaughan, 2011). Furthermore, fast gamma (~60–100 Hz) synchrony between CA1 and CA3 is found to increase during the encoding of novel object-place information (Zheng et al., 2016).

Studies on proteomes of hippocampal areas CA1 and CA3 were found to show a different level of expression for ~ 31% (532 proteins out of 1697 ones) after an open field exploration. In addition, memories for NOP and OPP explicitly altered CA1 and CA3 proteomes, in which the changes of protein expression were largely consistent in CA1 across the two forms of memory, but distinct in CA3. These results suggest that specialized proteomic roles of CA1 and CA3 areas contribute to recognition memory (von Ziegler et al., 2018).

The memory for object-place associations requires the involvement of the hippocampus. Lesions or NMDA-R blockade in the hippocampus disrupt OiP memory (Barker et al., 2007; Barker and Warburton, 2015; Good et al., 2007a). Post-sample infusions of the DNMT inhibitor RG108 or 5-aza-2'-deoxycytidine into the hippocampus impaired memory in the OiP, but not NOP, test, suggesting that hippocampal DNA methylation engages in the processing of object-place information (Scott et al., 2017).

3.3.3. Temporal order memory—Lesion studies have indicated the hippocampus to have a pivotal role in the processing of memory for object recency and/or for temporal order recognition (Albasser et al., 2012; Barker and Warburton, 2011b), but see (Tam et al., 2014). TOM memory seems to be mildly influenced when tested with a short 2 min interval in hippocampus-lesioned rats (Good et al., 2007a). Studies investigating the roles of different hippocampal subregions have shown that region CA1, but not CA3, is critical in the processing of temporal memory for objects (Hoge and Kesner, 2007). When temporal order judgment is involved in spatial alternation, e.g. when an object is moved to different locations at different time points, both, the CA1 and CA3 subregions were shown to be involved (Hunsaker and Kesner, 2008). These data suggest that the CA1 processes temporal information, irrespective of whether spatial or non-spatial stimuli are involved, while the CA3 only participates in this processing if a spatial component is present. Imaging data also show the CA1 to be activated during both spatial and nonspatial processing, while CA3 activation codes primarily information about place (Beer et al., 2013; Beer et al., 2014). Since both the CA1 (MacDonald et al., 2011; Pastalkova et al., 2008) and CA3 (Salz et al., 2016) cells have been identified for the processing of "*time*", an open question is how they contribute to episodic memory with respect to the "when" component. Distinct roles of CA1 and CA3 interacting with "when" is expected, as rats with the CA1 lesion showed deficits in a non-spatial temporal-order task if the inter-trial interval was 10, but not 3, seconds, while the CA3 lesioned rats had deficits in both intervals (Farovik et al., 2010). The hippocampus is important for the processing of memory for "*when*", which is fundamental for the construction of episodic memory.

3.3.4. Episodic-like memory—The hippocampus is essential for the formation and storage of episodic-like memory. Intra-hippocampus infusion of muscimol disrupted episodic-like memory, measured by licking behavior, and more *c-fos* and *zif-268* positive-cells were found in the hippocampal CA1, CA3 and dentate gyrus after the retrieval (Veyrac et al., 2015). In an episodic-like memory paradigm, in which social stimuli, i.e. female or dominant male animals, instead of objects were employed, mice displayed intact specific memory for "what-where-when" along with increased *Arc/Arg3.1* mRNA expression in the

hippocampus. In addition, microinjection of anisomycin into the hippocampus disrupted the consolidation of memory for “what-where-when” (Fellini and Morellini, 2013).

In the ELM2–1 test, the *c-fos* expression of hippocampal CA1 and dentate gyrus required for episodic-like memory was correlated with the *when* and *where* components, respectively (Castilla-Ortega et al., 2012; Castilla-Ortega et al., 2014). Furthermore, higher *Arc* RNA expression was found in the distal CA1 area for the processing of the *when* component, while the *where* component activated both CA1 and CA3 areas after the ELM2–1 test (Beer et al., 2018). In a nonmatching to location task, the distal CA3 (close to CA2), but not proximal CA3 (close to the dente gyrus), area was highly required (Flasbeck et al., 2018). These findings indicate that episodic memory is underpinned by segregated networks of spatial and non-spatial information along the proximo-distal axis of the hippocampus. In experiments studying the effects of chronic restraint stress and voluntary exercise on episodic-like memory and hippocampal neurogenesis, restraint disrupted neurogenesis and the *when* component, whereas exercise improved it and the *where* index of the ELM2–1 test (Castilla-Ortega et al., 2014). Pharmacological muscimol microinjections into the hippocampal CA1area disrupted the *where* and *when* components, while inactivation of the CA3/dentate gyrus spared the *when* component, but not the *where* component (Barbosa et al., 2012). Mice with hippocampal lesions were impaired in the *what*, *where* and *when* components in the ELM2–1 paradigm (DeVito and Eichenbaum, 2010). Transgenic mice with vasopressin 1b knockout exhibited deficient sociability and social novelty assessed by the three-chambered social test, and impaired *when* memory in the ELM2–1 test. Given that vasopressin 1b is highly expressed in the hippocampal CA2 area, the CA2 vasopressin 1b could be associated with social behaviors and episodic memory (DeVito et al., 2009), while its effects are likely independent of NMDAR as transgenic mice with selective NMDAR knockout in vasopressin 1b neurons showed intact social and object memories (Williams Avram et al., 2019).

Increased *zif-268* expression was found in the dorsal CA1 after exposure to the ELM2–2 paradigm in which rats showed intact *where*, but not *when* component (Barbosa et al., 2013). Rats with temporal lobe epilepsy induced by kainate treatment exhibited impaired episodic-like memory, assessed by the ELM2–2 test, along with disrupted theta coherence across the CA1 and dentate gyrus, but performance on tests of memory for *what* (NOP), *where* (OPP) or *when* (TOM) were not influenced (Inostroza et al., 2013b). In this epilepsy model, decreased theta-gamma (30–60 Hz) coupling in the hippocampal CA1 area was associated with the impaired episodic-like memory (Lopez-Pigozzi et al., 2016). In the ELM2–2 test, pre-sample intra-CA1 muscimol infusions disrupted the *interaction* as well as the *where* and *when* components (Drieskens et al., 2017). Importantly, CA3 lesioned rats exhibited intact NOP, TOM and spatial recognition memories, but were not capable of episodic-like memory in the ELM2–2 test, indicating that the CA3 region is critical for the integration of “what-where-when” components into an episodic-like memory (Li and Chao, 2008). Intra-CA3 infusion of lidocaine also impaired the performance of rats tested by a task of source memory, which is critical for identifying different episodes (Crystal et al., 2013). Distinct, but complementary, roles of differential hippocampal subregions and circuits are expected in the processing of episodic-like memory.

3.3.5. Glutamate—Glutamate plays an important role in hippocampal plasticity and object memory. For example, the extracellular glutamate content in the hippocampus was increased in the NOP test (Cohen et al., 2013; Stanley et al., 2012). NOP memory and hippocampal LTP were both impaired even several weeks later by a single systemic administration of MK-801, a NMDA-R blocker, in rats (Wieschollek and Manahan-Vaughan, 2013). The enhanced hippocampal LTD induced by the learning of novel objects can be blocked by the systemic administrations of the NMDA-R antagonist CPP or mGlu5-R antagonist MPEP (Goh and Manahan-Vaughan, 2013a). In an earlier study, mice with selective NMDA-R subunit 1 knockout in the hippocampal CA1 area exhibited NOP deficits (Rampon et al., 2000).

Pre-sample hippocampal infusions of AP5 disrupted NOP memory tested 3 hours, but not 5 minutes, later in rats (Baker and Kim, 2002). With manipulations of the number of objects used in the sample of the NOP test, pre-sample AP5 infusions into the hippocampus impaired memory when there were four, but not two, sample objects (Sugita et al., 2015). Pre-sample AP5 microinjections into the hippocampus impaired performance on OPP (Cassini et al., 2013), but not NOP (Barker and Warburton, 2015; Yamada et al., 2017). Pre-sample infusion of CNQX or AP5 into the rat postsubiculum also impaired long-term OPP, but not NOP, performance (Bett et al., 2013). Post-sample AP5 infusion into the hippocampus impaired OPP, while pre-test AP5 infusion had no influence, suggesting that the treatment influenced consolidation of information, but not retrieval processes (Yamada et al., 2017).

In a study that the strength of encoding (exposure to the sample from 2 – 5 times) and delay between trials (24 hours - 6 weeks) were manipulated, pre-test infusions of AP5 into the hippocampus disrupted NOP performance only when the memory was weak, while infusion of 2,3-Dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline-7-sulfonamide (NBQX), a potent AMPA-R antagonist, impaired the memory irrespective of the delays (Iwamura et al., 2016). The above results suggest that the hippocampal AMPA- and NMDA-R are important for OPP memory, while whether they account for NOP performance depends on the extent of memory load.

NMDA-R GluN1 and GluN2A levels were elevated in the hippocampus, but not in the PFC, after habituation to an open field and exploration in the NOP sample trial, while they did not change after the NOP test (Cercato et al., 2017), suggesting their roles in novelty discrimination of an environment. Reduction of NMDA-R surface dynamics in the dorsal hippocampus had no effect in the long-term (24 hours) OPP test (Potier et al., 2016). Maintenance of long-term OPP memory required GluA2/AMPA-R stabilization, as evidenced by intra-hippocampus infusions of peptides that intervene in the binding process of N-ethylmaleimide-sensitive factor to GluA2 (Migues et al., 2014). Likewise, post-sample hippocampal infusions of $GluA2_{3Y}$ or G2CT that interfered with the GluA2/AMPA-R removal, reinstated the forgotten OPP long-term memory and did not influence new OPP learning (Migues et al., 2016). In the ELM2–1 test, selective knockout of the NMDA-R subunit NR1 in the hippocampal CA1 region impaired *where*, but not *when*, memory in mice. In contrast, mice with the same knockout, but in the CA3 region, exhibited intact *where* and *when* memory (Place et al., 2012). This suggests that the CA1 NMDA signaling

is essential for the processing of spatial, but not temporal, information in an episodic-like context.

3.3.6. Dopamine—Simultaneous release of DA and NE was observed in the hippocampus during the OPP test, and catecholamine depletion in the dorsal hippocampus induced by 6-OHDA disrupted memory for OPP, but not NOP (Moreno-Castilla et al., 2017), indicating that hippocampal catecholaminergic neurotransmission has an active role in coding place of object.

In the SNOP test, infusions of the DA D1/2-R agonist apomorphine into the hippocampal CA1, but not CA3, disrupted short-term 3-min recognition of object location. The same infusions of apomorphine into the CA1 or CA3 region did not affect the object novelty (Vago and Kesner, 2008). Likewise, pre-sample microinjections of SCH23390 or SKF38393 into the hippocampus did not influence NOP memory tested 90 min or 24 hours later (Balderas et al., 2013). Thus, the hippocampal DA D1/2-R are key for the performance of location novelty, but not object novelty.

Pre-sample hippocampal infusion of the DA D1/5-R agonist SKF81297 improved long-term (24 hours interval) NOP memory (De Bundel et al., 2013), while that of SCH23390, a D1/5-R antagonist, impaired it (De Bundel et al., 2013). Pre-sample microinjections of SCH23390 into hippocampus did not affect OPP memory when tested 1 hour later (Savalli et al., 2015), but impaired long-term (24 hours) OPP memory (Moncada, 2017). The hippocampal DA D1/5-R mediate long-term NOP memory, while their roles in OPP memory are dependent on the extent of memory strength.

Post-sample trial microinjections of the D1-R antagonist SCH23390 and D3-R agonist 7-OH-DPAT, but not D2-R antagonist L-741.626, into the hippocampus impaired NOP when tested 1 hour later, whereas post-sample hippocampal infusions of SCH23390 had no effect on long-term NOP memory (Rossato et al., 2015; Rossato et al., 2013), although in another study an impairment by SCH23390 was reported (Furini et al., 2014). Post-sample microinjections of the D1-R agonist SKF81297, the D2-R agonist quinpirole and the D3-R antagonist SB277,011 into the dorsal hippocampus facilitated NOP when tested after 24 hours (Papp et al., 2017). Thus, the hippocampal DA D1-, D2- and D3-R are involved in NOP consolidation in a bidirectional manner, while D1-R showed variable effects.

In experiments on memory reconsolidation, in which the second sample trial can be considered as the test trial for NOP, pre-test infusions of SCH23390 into the dorsal hippocampal CA1 area showed no effects on long-term NOP memory (Rossato et al., 2015).

In a series of experiments studying the DAergic projections to the dorsal hippocampus, which originate primarily from the locus coeruleus, rather than ventral tegmental area (Kempadoo et al., 2016; Takeuchi et al., 2016), hippocampal opto-stimulation of the DA axon terminals from the locus coeruleus during learning facilitated long-term OPP memory. This facilitation effect was blocked by pre-sample trial infusions of SCH23390, but not of the β-adrenergic-R antagonist propranolol, into the dorsal hippocampus (Kempadoo et al., 2016). Although the ventral tegmental area-hippocampal DA projections are sparse, they

likely stabilize memory of searching for a spatial goal (McNamara et al., 2014) and regulate the hippocampal theta rhythm (Orzel-Gryglewska et al., 2015). Memory consolidation induced by contextual novelty was modulated by the DA release from the locus coeruleus, rather than ventral tegmental area, which is dependent on the hippocampal DA D1/5-R, but not adrenergic-R (Takeuchi et al., 2016).

3.3.7. Serotonin—Hippocampal plasticity has been shown to be mediated by 5-HT. For instance, hippocampal CA1 pyramidal neurons exhibited reduced spontaneous inhibitory postsynaptic currents (IPSC) after the application of SLV, a 5-HT6-R antagonist (de Bruin et al., 2016). Systemic post-sample administration of fluoxetine recovered long-term OPP memory, activated Akt/GSK-3β signaling in the hippocampus and increased hippocampal LTP in mice (Yi et al., 2018).

Post-sample, but not pre-sample or pre-test, infusions of TCB-2, a 5-HT2A-R agonist, into the dorsal hippocampal CA1 improved NOP when tested 24 hours later in mice. TCB-2 also enhanced the hippocampal glutamate levels and the mean firing rate of CA1 neurons (Zhang et al., 2016). The NOP-facilitating effect of the 5-HT1B-R agonist CP94253 in 5-HT1B-R adapter protein p11 knockout mice was prevented by overexpression of p11 selectively in the hippocampus (Eriksson et al., 2013). Post-sample infusions of RS67333, a 5-HT4-R agonist, or RS23597, a 5-HT4-R antagonist, into the dorsal CA1 area impaired spatial recognition tested by the SNOP paradigm (Nasehi et al., 2017).

Different subtypes of hippocampal 5-HT-R play distinct roles in object recognition, whereby 5-HT1A-, 5-HT1B- and 5-HT2A-R are involved in facilitation of consolidation, while 5-HT4-R seems to impair the processing of object consolidation and/or retrieval.

3.3.8. Acetylcholine—In the SNOP test including five different objects (Vago and Kesner, 2008), infusions of scopolamine and physostigmine, an acetylcholinesterase inhibitor, into the hippocampal CA3 area impaired and enhanced spatial and object recognition, respectively (Hunsaker et al., 2007b). Selective transection of dorsal CA3 projections in the fimbria, which constitutively blocks the MSvDB signals toward CA3, resulted in deficient spatial and object recognition in the SNOP test (Hunsaker et al., 2007b). Increased hippocampal ACh efflux was also found, regardless of whether a familiar or novel object was presented (Stanley et al., 2012).

Pre-sample infusions of nicotine into the dorsal hippocampus facilitated long-term NOP and OPP memories when tested 72 hours later in rats (Melichercik et al., 2012). Post-sample microinjections of scopolamine into the hippocampus disrupted NOP memory after 90 min, but not 24 hours; long-term NOP memory was also not influenced when the injection was made 160 min after the sample trial or 90 min before the test trial (Balderas et al., 2012). Pre-test infusions of scopolamine into the dorsal CA1 area did not affect NOP memory, but reduced the overall object exploration time (Rashid and Ahmed, 2019). The hippocampal ACh-R play key roles in memory consolidation, with nicotinic and muscarinic ACh-R being related to facilitation and disruption of mnemonic storage, respectively.

The interaction between cholinergic and NMDA systems contributes to memory. In cultured hippocampal neurons, for example, co-application of choline and NMDA/glycine caused larger currents than the application of NMDA/glycine alone; choline enhanced NMDA-R-mediated LTP of miniature excitatory postsynaptic currents (EPSC). Intervention with the interaction between the nicotinic α7 ACh-R and NMDA-R blocked these effects *in vitro*, and disrupted NOP memory in mice (Li et al., 2013). Application of the nicotinic α7 ACh-R agonist FRM-17874 facilitated NOP in rats and dose-dependently enhanced the theta oscillation induced by electrical stimulation in the rodent hippocampus (Stoiljkovic et al., 2015).

3.3.9. Histamine—The tuberomammillary nucleus of the posterior hypothalamus, the origin of histaminergic neurons, projects axons to wide areas of the brain; e.g. histamine H1-, H2- and H3-R are found in the cortex, hippocampus and amygdala (Esbenshade et al., 2008; Panula et al., 1984; Ryu et al., 1995; Watanabe et al., 1984). In histamine H1-R and H2-R knockout mice, LTP in the hippocampus CA1 area was decreased together with impairment of NOP memory (Dai et al., 2007).

The hippocampal histamine-R play a critical role in object memory consolidation: Post-sample infusions of the histamine H1-R antagonist pyrilamine, the H2-R antagonist ranitidine or the H3-R agonist imetit into the hippocampal CA1 area impaired long-term NOP memory (24 hours) when infused 30 min or 2 hours later, but not when applied immediately or 6 hours later (da Silveira et al., 2013). Conversely, the histamine H1-R agonist pyridylethylamine, the H2-R agonist dimaprit and the H3-R antagonist thioperamide had no effect on NOP consolidation when infused into the CA1 (da Silveira et al., 2013).

3.3.10. Norepinephrine—The locus coeruleus located in the brainstem is a cluster of adrenergic neurons that release NE across the central nervous system. It is well-known that NE modulates multiple functions, including arousal, attention, stress, and learning and memory (Benarroch, 2009; Schwarz and Luo, 2015). Systemic administration of propranolol, a β-adrenergic antagonist, blocked the learning-induced hippocampal LTD and spatial object recognition in freely moving mice (Goh and Manahan-Vaughan, 2013b).

The rat hippocampal NE levels were found to increase after object exploration (Mello-Carpes et al., 2016). Post-sample infusions of the β-adrenergic antagonist timolol into the hippocampal CA1 area disrupted long-term NOP memory in rats (Furini et al., 2010; Mello-Carpes et al., 2016; Mello-Carpes and Izquierdo, 2013). Interestingly, intra-CA1 infusions of NE reversed the long-term NOP memory impairment induced by infusions of muscimol into the locus coeruleus (Mello-Carpes and Izquierdo, 2013). Post-sample infusions of NE into the rat CA1 region also promoted NOP memory tested 21 days later (Mello-Carpes et al., 2016). Thus, NE systems in the hippocampal CA1 control long-term NOP consolidation.

3.3.11. Cannabinoid—The endocannabinoid system critically mediates development, synaptic plasticity, cognition and neuropsychiatric disorders through cannabinoid-R, endocannabinoids and the enzymes regulating the synthesis and degradation of the endocannabinoids. The G-protein-coupled cannabinoid 1-R is enriched in axonal terminals in the brain, while cannabinoid 2-R is mainly, but not exclusively, expressed in the periphery

system (Lu and Mackie, 2016; Lutz et al., 2015). Application of JWH-018, a synthetic cannabinoid 1/2-R agonist, decreased potassium-evoked glutamate and GABA release and LTP in hippocampus slices (Barbieri et al., 2016; Basavarajappa and Subbanna, 2014). Mice with selective knockout of cannabinoid 1-R in the GABAergic neurons, exhibited disruption of NOP (30 min) memory, and facilitation of spontaneous IPSC in the CA1 pyramidal neurons *in vitro* (Albayram et al., 2016). Furthermore, knockdown of the cannabinoid 1-R-interacting protein 1 in the mouse hippocampus increased cell proliferation and neuroblast differentiation in the dentate gyrus and improved NOP memory (Jung et al., 2017).

Intra-hippocampus infusions of WIN 55,212–2, a non-selective cannabinoid-R agonist, dose-dependently disrupted the performance in the OPP, but not NOP, test in rats (Suenaga and Ichitani, 2008). Post-sample infusions of WIN 55,212–2 or VDM-11, an endocannabinoid membrane transporter inhibitor, into the hippocampal CA1 region impaired long-term, but not short-term, NOP memory in a dose-dependent manner. Similar effects were found by the CA1 infusion of the cannabinoid 1-R agonist ACEA, but not the cannabinoid 2-R agonist JWH-015 or palmitoylethanolamide, an endogenous fatty acid amide with affinity to cannabinoid-R GPR55 and GPR119, suggesting a role of hippocampal cannabinoid 1-R in NOP consolidation (Clarke et al., 2008). Microinjections of the cannabinoid 1-R antagonist AM251 into the CA1 region facilitated object novelty tested by the SNOP paradigm (Nasehi et al., 2017).

The cannabinoid 1-R in the hippocampus play distinct roles in the modulation of NOP and OPP memory, as evidenced by memory being impaired and improved through pharmacological activation and blockage of the R, respectively.

3.3.12. Signaling pathway—Many molecular pathways within the hippocampus are involved in object memory. For instance, inhibition of d-amino acid oxidase through d-serine modulation, augmented NMDA-R-mediated long-term potentiation (LTP) in the hippocampus *ex vivo* and improved long-term NOP memory *in vivo* (Hopkins et al., 2013). Intra-hippocampal infusions of rapamycin, an inhibitor of mTOR signaling, either pre- or post-sample, impaired NOP memory tested 24 hours later, suggesting that mTOR mechanisms in the hippocampus are underlying long-term object memory (Jobim et al., 2012), compatible with previous findings (Myskiw et al., 2008). Intra-hippocampal infusions of PD98059, a selective MEK inhibitor, disrupted long-term NOP memory in mice (Nagai et al., 2007). The RGS14 gene knockout mouse exhibited improved NOP memory and facilitation of LTP in the CA2, but not CA1, area. This effect is dependent upon the ERK/MAPK pathways, given that facilitated LTP in the CA2 was blocked by U0126, a MEK inhibitor (Lee et al., 2010). Expression of the nuclear factor kappa B (NF-kB) and the immediate-early gene zif268 were increased after object exploration, and post-trial intra-hippocampal inhibition of NF-kB or zif268 impaired NOP memory (Zalcman et al., 2015). Object exploration also increased the expression of the immediate-early genes Nr4a1 and Nr4a2, while intra-hippocampal knockdown of either one impaired long-term OPP (24 hours) memory (McNulty et al., 2012). Post-sample infusions of zeta inhibitory peptide into the rat hippocampus impaired NOP memory (Hales et al., 2015). Intra-hippocampus injection of the AAV vector carrying either a negative or active form of Rac1, facilitated and impaired NOP memory, respectively, suggesting that Rac1 activity in the hippocampus

dually controls NOP memory (Liu et al., 2016). Inactivating the atypical protein kinase C isoform M zeta (PKMζ) in the dorsal hippocampus abolished memory for OPP, but not NOP (Hardt et al., 2010); these effects were regulated by glutamate subunit 2-dependent AMPA-R (Migues et al., 2010).

Object exploration elevated the rat hippocampal BDNF levels (Furini et al., 2010; Mello-Carpes et al., 2016), and selective BDNF deletion in the mouse hippocampus disrupted NOP memory (Heldt et al., 2007). Post-sample intra-hippocampus BDNF infusions were found to compensate OPP deficits induced by anisomycin, and hippocampal BDNF infusions facilitated long-term OPP memory (Ozawa et al., 2014), suggesting hippocampal BDNF is involved in protein synthesis for spatial memory consolidation. Increased expression of BDNF in the hippocampal CA1 with the transduction of AAV9-BDNF, elevated the phosphorylation level of CaMKII, CREB, tropomyosin receptor kinase (TrkB) and p38 MAPK, and facilitated long-term OPP, but not NOP, memory (Wang et al., 2017b). Thus, BDNF signaling pathway in the hippocampus mediates NOP and OPP memory.

Post-sample hippocampal infusions of histone acetylase inhibitors decreased histone acetylation and impaired NOP memory (Federman et al., 2013; Zhao et al., 2012), while the infusion of a HDAC inhibitor had the opposite effects (Federman et al., 2013). Longer learning of the sample trial of the NOP test increased hippocampal histone H3 acetylation and persistence of NOP memory, which could be prevented by NF-kB inhibition (Federman et al., 2013). OPP memory was enhanced by post-sample microinjections of the HDAC inhibitor sodium butyrate into the dorsal hippocampus (Roozendaal et al., 2010). HDAC3-*flox* mice injected with AAV-*Cre* recombinase into the hippocampal CA1 region to selectively deplete HDAC3 in CA1, showed enhanced long-term OPP memory. Similar results were found in mice with the intra-CA1 infusions of RGFP136, a selective HDAC3 inhibitor (McQuown et al., 2011). The deacetylase domain of HDAC3 in the hippocampus was also found to be critical for long-term OPP memory in mice (Alaghband et al., 2017). Disrupted long-term OPP, but not NOP, memory, along with impaired hippocampal LTP and reduced histone H2B, H3 and H4 acetylation, were found in the CREB-binding protein-*flox* mice microinjected with AAV-*Cre* into the dorsal hippocampus to produce hippocampal CREB-binding protein depletion (Barrett et al., 2011).

3.3.13. Short summary—Although the involvement of hippocampus in the NOP test is controversial (see 3.3.1), the hippocampus is essential for the processing of long-term NOP consolidation and retrieval. In addition, the hippocampus cardinally regulates the processing of OPP, OiP and episodic-like memories. Distinct neurotransmitter systems in the hippocampus have complementary and interactive roles in the regulation of different object exploration tests. The hippocampal DA, ACh and NE bi-directionally modulate NOP and OPP memories, while glutamate, 5-HT, histamine and cannabinoids are also engaged. The functions of hippocampal neurotransmitter systems are governed by different subtypes of receptors. Details of findings of substances injected locally into the hippocampus (points 3.3.5–11) are listed in Table 4.

4. The functional hippocampal-cortical network of episodic memory

As the mPFC, LEC and hippocampus have major functions in the processes governing memory for object, place, time and their integration, we thus dissect their anatomical, electrophysiological and behavioral roles in the context of episodic memory.

4.1. The pathways between the prefrontal cortex, entorhinal cortex and hippocampus

There are strong multi-synaptic (indirect pathway) connections between the mPFC and hippocampus, but monosynaptic projections (direct pathway) also exist (Rajasethupathy et al., 2015). A direct hippocampus-PFC pathway originates from the ventral hippocampal CA1 area and subiculum onto the mPFC, while sparse projections from the intermediate third of the hippocampus also exist (Cenquizca and Swanson, 2007; Jay and Witter, 1991). This hippocampus-mPFC pathway makes synaptic contact both with glutamatergic pyramidal neurons and GABAergic interneurons within the mPFC (Gabbott et al., 2002; Jay et al., 1992; Tierney et al., 2004). The majority studies have focused on the dorsal hippocampus, and thus, the understanding of functions of the hippocampal ventral compartment is not as solid as that of its dorsal part. The dorsal and ventral hippocampus exhibit functional heterogeneity (Fanselow and Dong, 2010). For example, the ventral CA1 cells required stronger afferent stimulation to elicit action potentials, showed lower neuronal excitability and attenuated LTP induced by theta burst stimulation than the dorsal CA1 cells. The levels of NMDA GluN1-, GluN2-, mGlu1-, mGlu2/3- and DA D1-R were higher, but $GABA_A$-R was lower, in the ventral than dorsal hippocampus, while mGlu5-, $GABA_B$- and DA D2-R were unchanged across the hippocampus (Dubovyk and Manahan-Vaughan, 2018). The functional topography along the hippocampus dorsal-ventral axis likely affects the interaction with the mPFC, which receives strong projections from the ventral hippocampus.

A direct monosynaptic projection from the mPFC back to the hippocampus could not be reveal until recently, when a projection from the prefrontal cortical ACC to the dorsal hippocampal CA1 and CA3 regions in mice was found through viral vector tracing. This monosynaptic ACC-hippocampus projection was further examined by transferring channelrhodopsin-2 (ChR2) into the ACC, and by patch-clamp recording *in vitro* dorsal CA1 and CA3 neurons. It has found that light-stimulation of the axonal terminals of ACC was sufficient to incur EPSC and evoked action potentials in the CA1 and CA3 neurons, but not the dentate gyrus. This monosynaptic projection is also functionally essential for memory retrieval, as assessed by contextual fear conditioning (Rajasethupathy et al., 2015). Thus, direct and mutual information processing between the PFC and hippocampus exists in rodents. The intermediate and ventral hippocampus send projections to the mPFC, which presumably transfers hippocampus-relevant information to the PFC. The prefrontal cortical ACC projects back to the hippocampus and delivers PFC-relevant information onto the hippocampus (Fig. 4).

The indirect communication between the PFC and hippocampus was via other substrates to form many multi-synaptic routes. The nucleus reuniens (NR) in the medial thalamus, the perirhinal cortex and LEC are mutually connected with the PFC and hippocampus (Apergis-Schoute et al., 2006; Burwell and Amaral, 1998a; Hoover and Vertes, 2007; Varela et al.,

2014). Anatomical interconnections are also found among the NR, perirhinal cortex and LEC (Burwell and Amaral, 1998a, b; Varela et al., 2014). Besides these regions, other neural substrates that project to both mPFC and hippocampus include the amygdala, ventral tegmental area, MSDB, and hypothalamus (Hoover and Vertes, 2007; Varela et al., 2014). DA and ACh neurotransmission play critical roles in the regulation of memory via the ventral tegmental area and MSDB projections to the PFC-hippocampus-associated circuits (Hasselmo, 2006; Lisman and Grace, 2005). Importantly, a subpopulation of single NR and LEC neurons sends axonal collaterals to both mPFC and hippocampus, implicating that the NR and LEC can directly and simultaneously modulate the activities of mPFC and hippocampus (Hoover and Vertes, 2012; Varela et al., 2014). The inhibitory projections from the LEC, but not MEC (since the projections are sparse (Melzer et al., 2012), to the hippocampal CA1 area form a disinhibition mechanism which blunts NOP processing (Basu et al., 2016). Thus, the indirect PFC-hippocampus pathway could engage in the functions required for the interaction between PFC and hippocampus. For example, the PFC-NR circuit is proposed to modulate memory generalization versus specification, at least in hippocampus-dependent contextual fear memory (Xu and Sudhof, 2013). The interplay between the mPFC and medial thalamus is also critical for TOM and OiP, but not NOP, tests (Cross et al., 2012). Electrical stimulation of the EC has been found to reduce PFC pyramidal cellular activity (Valenti and Grace, 2009), and to enhance neurogenesis in the dentate gyrus of the hippocampus (Stone et al., 2011). Brain activities, measured by fMRI, were increased in the rat mPFC and hippocampus by 5–20 Hz electrical stimulation of the LEC (Krautwald et al., 2019). Imaging studies have also indicated that the LEC-CA1 pathway is recruited for the processing of exploration of familiar objects and of object-recency, while the pathway of LEC-dentate gyrus-CA3 is activated for the processing of recognition of novel objects and for object-recency (Aggleton et al., 2012; Kinnavane et al., 2014; Olarte-Sanchez et al., 2014). Evidence also shows increased functional connectivity of hippocampal CA1, CA3, insular cortex, perirhinal cortex and mPFC formed by the NOP test (Tanimizu et al., 2018). The interaction between the mPFC and LEC is crucially involved in episodic-like memory in rats (Chao et al., 2016a). While the direct PFC-hippocampal and indirect PFC-NR/perirhinal/LEC-hippocampal pathways form anatomical loops for memory, the functional distinctions between the direct and indirect pathways are elusive, particularly in the context of episodic memory.

4.2. Functional connectivity between the prefrontal cortex and hippocampus

4.2.1. Electrophysiological studies—Electrophysiological and behavioral evidence has implicated the PFC-hippocampus circuits in the processing of memory. For instance, a portion of the PFC neurons were found to be coupled to the theta rhythm (4–10 Hz) of the hippocampus and to best match with a delay of approximately 50 ms. This illustrates that the PFC-hippocampal projections generate an oscillatory synchronization and supports the concept of a directional pathway of hippocampus towards the PFC as focal for information processing (Siapas et al., 2005). In a reward-based Y-maze learning paradigm, the theta coherence between the PFC and hippocampus was increased, especially after rats had learned how to reliably procure food (Benchenane et al., 2010). Lesions in the ventral hippocampus disrupted the PFC activity for anticipating a spatial goal (Burton et al., 2009), indicating that the hippocampus processes and guides the PFC with respect to spatial

information. In a complex experimental design, rats were trained to discriminate object-reward pairings based on different contexts: Object A, but not object B, was paired with food in context 1, with the opposite condition in context 2. Local field potentials of the PFC and hippocampus were recorded during the onset of exploring the contexts and objects. The strength of theta synchronization between the PFC and hippocampus was shifted based on different onsets. Theta oscillations in the hippocampus precede those in the PFC during the onset of contextual exploration, while the prefrontal cortical theta precedes that in the hippocampus during the onset of object exploration (Place et al., 2016). In addition, the PFC-hippocampus theta oscillations were enhanced after an error made in a paired associative learning task, and were primarily directed by the PFC to hippocampus information flow. By contrast, the opposite information flow was found after correct answers together and with stronger alpha/beta oscillations (Brincat and Miller, 2015). In humans, the PFC-hippocampus theta coherence was also increased in an inferential task which required participants to integrate associations that shared common features (Backus et al., 2016). Alternatively, an oscillation varying between 2–5 Hz could also be involved in the PFC-hippocampus coupling (Fujisawa and Buzsaki, 2011), which can be modulated by the NR. Microinjection of lidocaine into the NR decreased the coherence of 2–5 Hz, but not theta, between the PFC and hippocampus in rats (Roy et al., 2017). These findings suggest that the direct and indirect pathways of PFC-hippocampus could be distinctly associated with the theta and 2–5 Hz PFC-hippocampus synchronization, respectively. The hippocampus apparently generates a spatiotemporal event and contacts the PFC for information, while the role of PFC is that of an executor that guides the hippocampus in correctly retrieving that event. Such reasoning receives support from brain imaging studies indicating strong links between the PFC and medial temporal lobe during episodic encoding (Schott et al., 2011; Schott et al., 2013), and both regions are involved in the integration of temporal-context memory (Jenkins and Ranganath, 2010; Naya et al., 2017; Tubridy and Davachi, 2011).

4.2.2. Lesion and inactivation studies—The application of *disconnection procedures* together with behavioral tests has proven useful in exploring the causality of the mPFC-hippocampus interaction in the control of episodic memory. The basic proposition of the disconnection approach is that, if two brain areas interact for a specific function, disrupting one of the areas in one hemisphere combined with a simultaneous disruption of the other area in the opposite hemisphere (i.e. *disconnecting* the circuit at two different levels) should lead to a functional deficit. Disconnecting the PFC-hippocampus pathway did not influence performance in NOP and OPP tests, either by lesions (Barker and Warburton, 2011b) or infusions of NBQX or AP5 before the sample trial (Barker and Warburton, 2015). However, disconnection of the PFC and hippocampus disrupted TOM and OiP (remembrance for altering relative object-location associations) memories (Barker and Warburton, 2011b). Disconnected inactivation of the mPFC and hippocampus with pre-sample NBQX or AP5 infusions impaired OiP performance, independent of time delay. Retrieval of OiP memory was dependent on the PFC-hippocampus AMPA-R, but not NMDA-R (Barker and Warburton, 2015). Furthermore, pre-test infusions of NBQX into the unilateral PFC and hippocampus with the disconnection approach impaired the *where* and *when* components of the ELM4–2 test (Barker et al., 2017). These findings suggest that the interplay between the PFC and hippocampus is critical for “when” and “what-where-when” memories.

A meta-system of episodic-like memory which integrates the "what", "where" and "when" component memories: The question that follows is whether the PFC-hippocampus pathway directly contributes to episodic memory *per se* or merely to the individual memory systems for *what*, *where* or *when* memory, given that, by logic, an impairment of one of the components should cause a failure of episodic memory. To investigate this issue, we conducted an episodic-like memory test along with separate tests for the components "what", "where" and "when" in the same animals. The mPFC and dorsal hippocampus CA1 or CA3 regions were disconnected by employing the ELM2–2 test (For details see (Chao et al., 2017; de Souza Silva et al., 2016). When the PFC-CA1 circuit was interrupted, the ability to integrate distinct components into an episodic-like memory was impaired. Furthermore, performance in the OPP test (*where*) was disrupted, whereas memories for NOP (*what*) and TOM (*when*), were intact. The disruption of episodic-like memory could not have resulted from the impairment of object location memory since the PFC-CA1 disconnected animals showed intact spatial recognition in the ELM2–2 test (positive *where* index). This argues that they were not incapable of recognizing different locations. These findings indicate that the PFC-CA1 circuit is critically involved in the processing of episodic-like memory itself (Chao et al., 2017). By contrast, disconnecting the PFC-CA3 circuit also impaired performance in the ELM2–2 test, but did not interfere with performance in the individual NOP, OPP and TOM tests. Pharmacological inactivation of the PFC in one hemisphere with CNQX, but not with AP-5, combined with lesions of CA3 in the opposite hemisphere (disconnecting the CA3 and PFC gultamatergic circuit) disrupted episodic-like memory (de Souza Silva et al., 2016).

These results lead to the conclusions regarding the neurobiological bases of episodic-like memory: (a). Since the disconnected PFC-CA3 circuit resulted in intact individual memory for *what*, *where* and *when*, but disrupted episodic-like memory, it follows that episodic-like memory is not simply a combination of "what", "where" and "when" memories, but a meta-system that integrates these components into episodic-like memory. (b). The PFC AMPA/kainate-R, but not NMDA-R, are involved in the processing of episodic-like memory. These results are compatible with the finding that the AMPA-R, but not NMDA-R, in the PFC are essential for the learning and memory of object-place associations (Barker and Warburton, 2008, 2015; Tse et al., 2011), probably due to the fast synaptic transmission provided by AMPA-R. (c). Disconnecting the PFC-CA1 and PFC-CA3 pathways revealed differential effects on episodic-like memory, indicating distinct functional roles of the PFC-CA1 versus -CA3 pathways.

The indirect PFC-hippocampus pathway also plays an important role in the processing of episodic-like memory. For instance, the NR mutually connects with the PFC and hippocampus and has been proposed to have an active role in the processing of memory. The NR-lesioned rats exhibited intact NOP, OPP and short-term OiP memories, but long-term OiP memory was impaired. Furthermore, the muscarinic and nicotine ACh-R, but not NMDA-R, of the NR can modulate the encoding of OiP memory (Barker and Warburton, 2018). Alternatively, the LEC, which is essential for object-associations (Wilson et al., 2013c), projects mutually to the CA1, CA3 and PFC. In order to test whether the indirect pathway is causally involved in episodic-like memory, the PFC-LEC circuit was

disconnected (Chao et al., 2016a). As expected, memory tested by the ELM2–2 test was deficient, suggesting the PFC-LEC circuit is indispensable for episodic-like memory. This pathway is also engaged in the processing of object-associated identity, location and context information, but not in NOP, OPP and TOM (Chao et al., 2016a).

4.2.3. Functional circuits—Attempts to dissect functions of differential neuronal circuits are progressing with the development of advanced biological tools, such as chemo- and opto-genetics. Barker et al. (2017) selectively inactivated the circuits from the posterior-dorsal or intermediate CA1 projecting to the mPFC in rats. In the ELM4–2 test, inactivation of the posterior-dorsal CA1 to PFC pathway impaired the *when*, but not *where*, component of episodic-like memory, while inactivation of the intermediate CA1-PFC pathway disrupted the *where*, but not *when*, component. Furthermore, the posterior-dorsal CA1 to PFC pathway was crucial for the memory for temporal-order, but not for NOP, OPP and OiP. In contrast, the intermediate CA1 to PFC pathway was important for OiP memory, but not for NOP, OPP and temporal-order. The findings pinpoint that the CA1 projection to PFC pathway is functionally divergent, with the posterior-dorsal and intermediate circuits accounting for the processing of temporal and inter-item locational information, accordingly (Barker et al., 2017).

Different extents of episodic-like memory deficits were observed, depending on the region disconnected in the studies of disconnecting the mPFC either from the CA1, CA3 or LEC (Chao et al., 2016a; Chao et al., 2017; de Souza Silva et al., 2016) (Table 5). The results indicate that there is a bias for the episodic-like information to be processed in the direct pathways than indirect PFC-hippocampal ones. Using the ELM2–2 test, it was found that the w*here* component was still functional, although weakened after disconnecting the PFC-LEC pathway, which spared the direct CA3-CA1-PFC circuit. Disconnection of the PFC-CA1 pathway, while preserving the indirect CA3-LEC-PFC circuit, impaired the *interaction* index. When the PFC-CA3 pathway was disconnected, the *interaction*, as well as the *where* and *when* indexes were disrupted. These results reveal that, although the CA1-PFC pathway was preserved, episodic-like and associated spatial memories were still impaired, which highlights the role of the interplay between the PFC and CA3 in the processing of episodic information. In sum, these findings imply that (a). Processing of episodic information is more actively involved in the direct PFC-hippocampal pathway than in the indirect pathway. (b). Both the CA1 and CA3 regions are cardinal in the integration of “what-where-when” components into episodic-like memory. (c). The direct pathway from the CA1 to the PFC alone may not to be sufficient for coding episodic-like memory unless it receives additional inputs from the CA3 region. However, the direction of information flow in these studies is hard to ascertain, since the connections are ablated. Experiments with precise circuity control, e.g. optogenetics, are necessary to establish the distinct involvement of the links between CA1 and CA3 to the PFC and of the direct versus indirect hippocampal-PFC connections in the control of episodic-like memory. Recent human imaging studies shed light on the distinct but complementary characteristics of CA1 and CA3 in episodic memory (Copara et al., 2014; Dimsdale-Zucker et al., 2018). Nevertheless, the disconnection studies have contributed new insights into the neural networks that determine episodic-like memory

and its component memory systems of object recognition in space and time, with emphasis on the cirtical involvement of the direct and indirect PFC-hippocampal pathways (Fig.5).

5. Conclusion

Episodic-like memory has been investigated and characterized as a prototype of episodic memory in the fields of behavioral neuroscience, psychopharmacology and cognitive psychology. The *training-free* episodic-like memory tests exploit the spontaneous object exploration which is shown by many species as behavioral measures, and thus, avoid using strong positive and negative reinforcements and extensive training procedures. These paradigms combine the properties of the NOP, OPP and TOM tests in the attempt to decipher the neurobiological mechanisms that underlie episodic-like memory. The direct and indirect pathways between the mPFC and hippocampus employ distinct, but complementary, functions to structure the “what”, “where” and “when” components that subserve episodic memory. Moreover, different neurotransmitter systems within the mPFC and hippocampus behave synergistically during the learning, storage and retrieval processes inherent in the NOP, OPP and TOM tests. The anatomical and functional connections between the mPFC, LEC and hippocampus inclusively, but not exclusively, underpin the formation of episodic-like memory. A meta-system of episodic-like memory which integrates the “what”, “where” and “when” component memories likely comprises the hippocampal CA1/CA3-prefrontal cortical circuitry.

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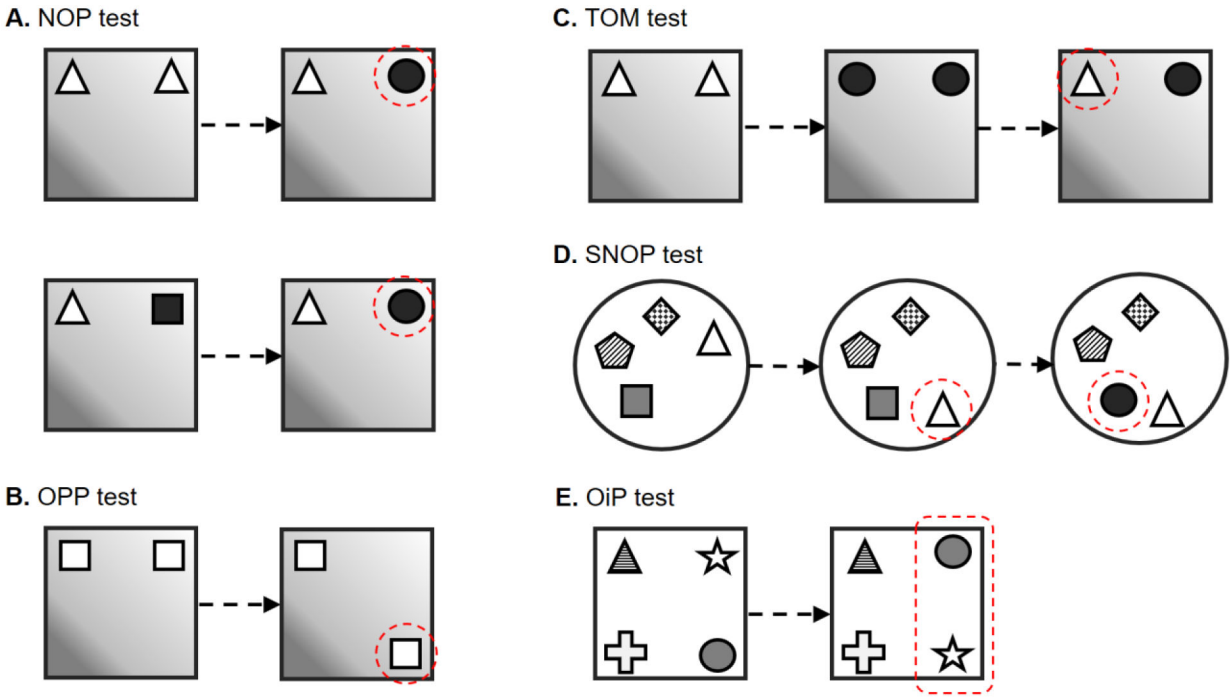

Figure 1.

Schematic diagrams of spontaneous object exploration paradigms. (A) Novel object preference (NOP) test. (B) Object place preference (OPP) test. (C) Temporal-order preference memory (TOM) test. (D) Spatial and non-spatial object preference (SNOP) tests. (E) Object-in-place preference memory (OiP) test. Dashed circles indicate the exploratory preference of animals in nature, compared to the other object(s) in that specific trial.

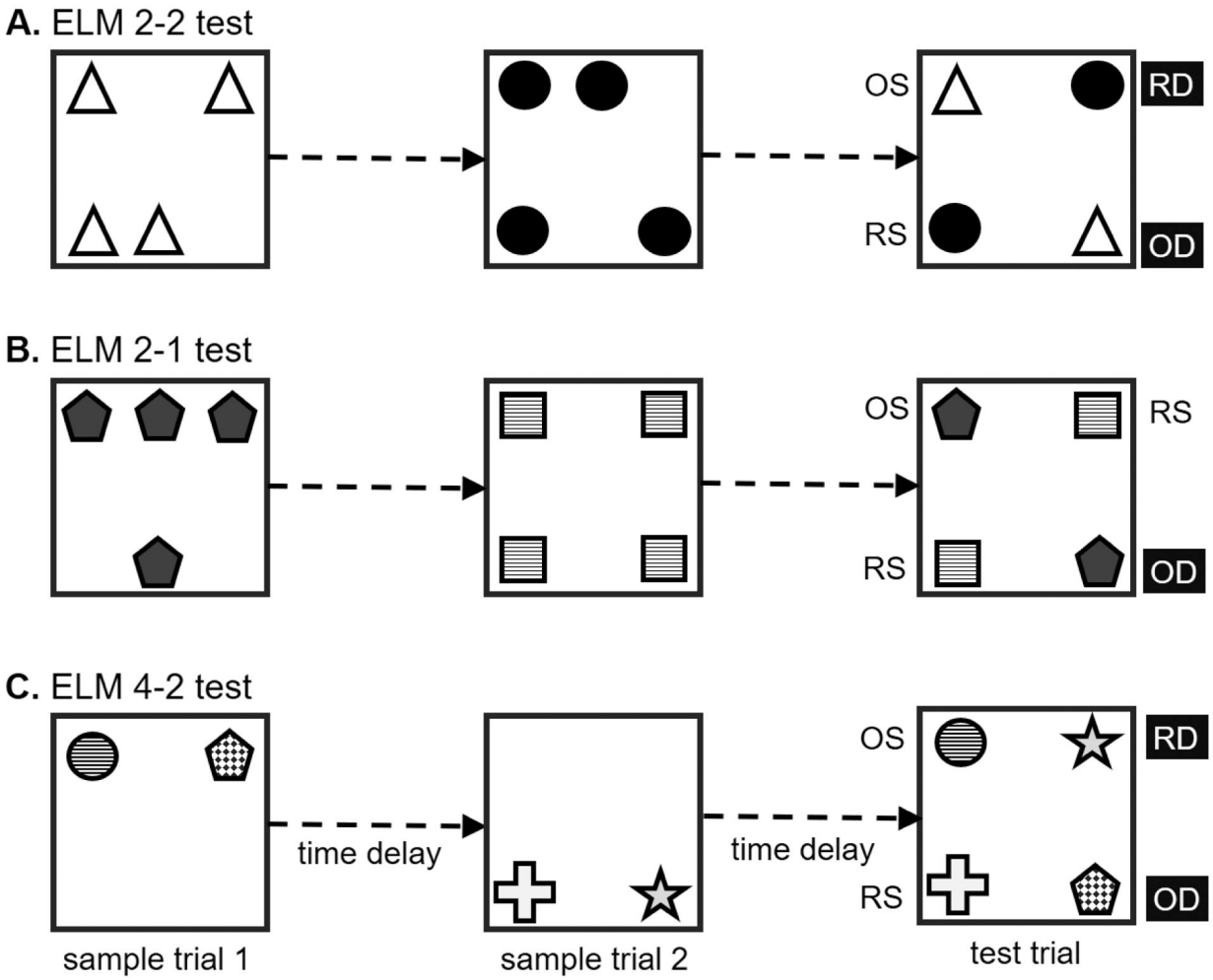

Figure 2.

Schematic presentation of the training-free episodic-like memory paradigms with the use of spontaneous object exploration. (A) Test with two sets of objects and displacement of two objects in the test trial (ELM2–2). Two sets of objects, each with four copies, are presented separately at different time points (sample trial 1 and 2). After a delay, two objects from each set are presented together either placed at the same or different location(s). Thus, different spatiotemporal features are attributed to the objects, namely, one older-familiar object at the location that was occupied before (OS), one older-familiar object at a novel location (OD), one recent-familiar object at the location that was occupied before (RS) and one recent-familiar object at a novel location (RD). (B) Test with two sets of objects and displacement of one object in the test trial (ELM2–1). The ELM2–1 paradigm is similar to the ELM2–2 test except that only one object is displaced in the test trial, i.e. the OD. (C) Test with four distinct objects and displacement of two objects in the test trial (ELM4–2). The object arrangement of this test is comparable to the ELM2–2 test but involves four distinct objects.

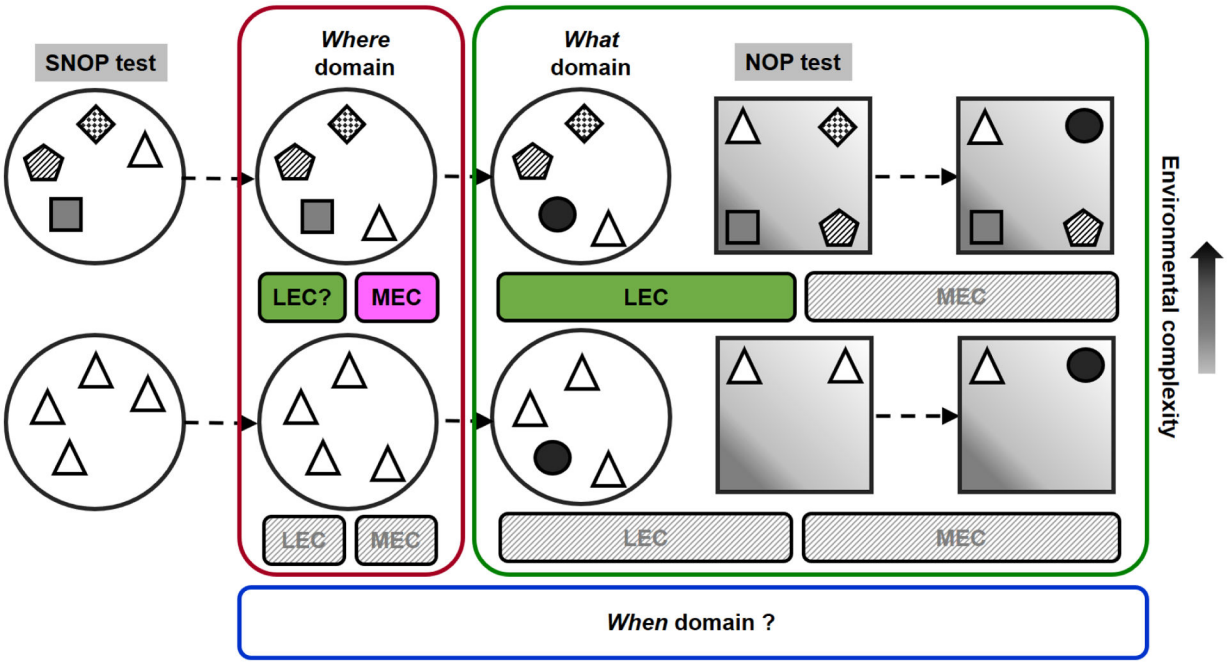

Figure 3.

The roles of lateral entorhinal cortex (LEC) and medial entorhinal cortex (MEC) in the spatial and non-spatial object preference (SNOP) and novel object preference (NOP) tests. Both regions are not required in simple situation (identical objects). In complex situation (4 distinct objects), the LEC, but not MEC, is essential for the processing of object recognition (*what*), while the MEC is essential for spatial recognition (*where*). Lesions of the LEC are reported to disrupt spatial recognition (van Cauter et al., 2013), but see (Rodo et al., 2017). How the LEC and MEC interact with time (*when*) remains underexplored since the majority of the studies applies short retentions only (less than 10 minutes; unclear for longer delays).

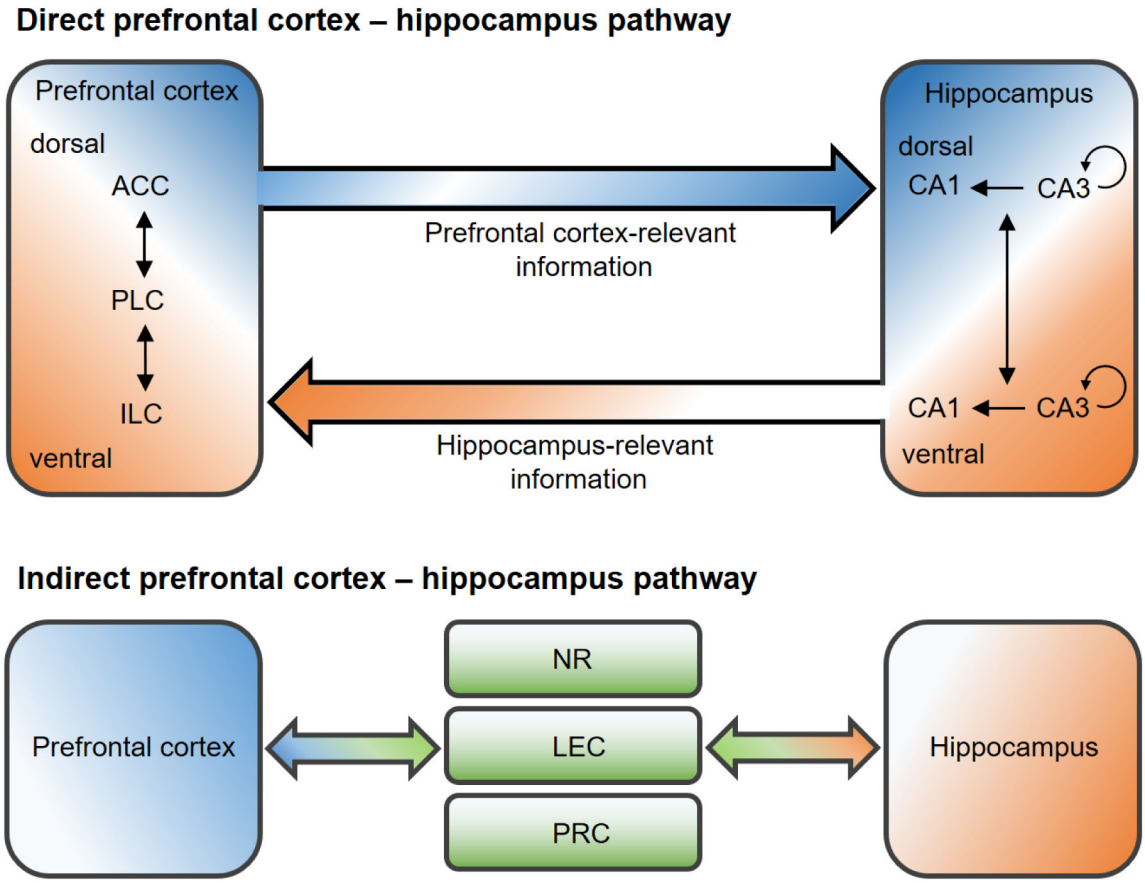

Figure 4.

Diagram of direct (top) and indirect (bottom) neuroanatomical pathways between the prefrontal cortex and hippocampus. ACC: anterior cingulate cortex; PLC: prelimbic cortex; ILC: infralimbic cortex; NR: nucleus reuniens; LEC: lateral entorhinal cortex; PRC: perirhinal cortex.

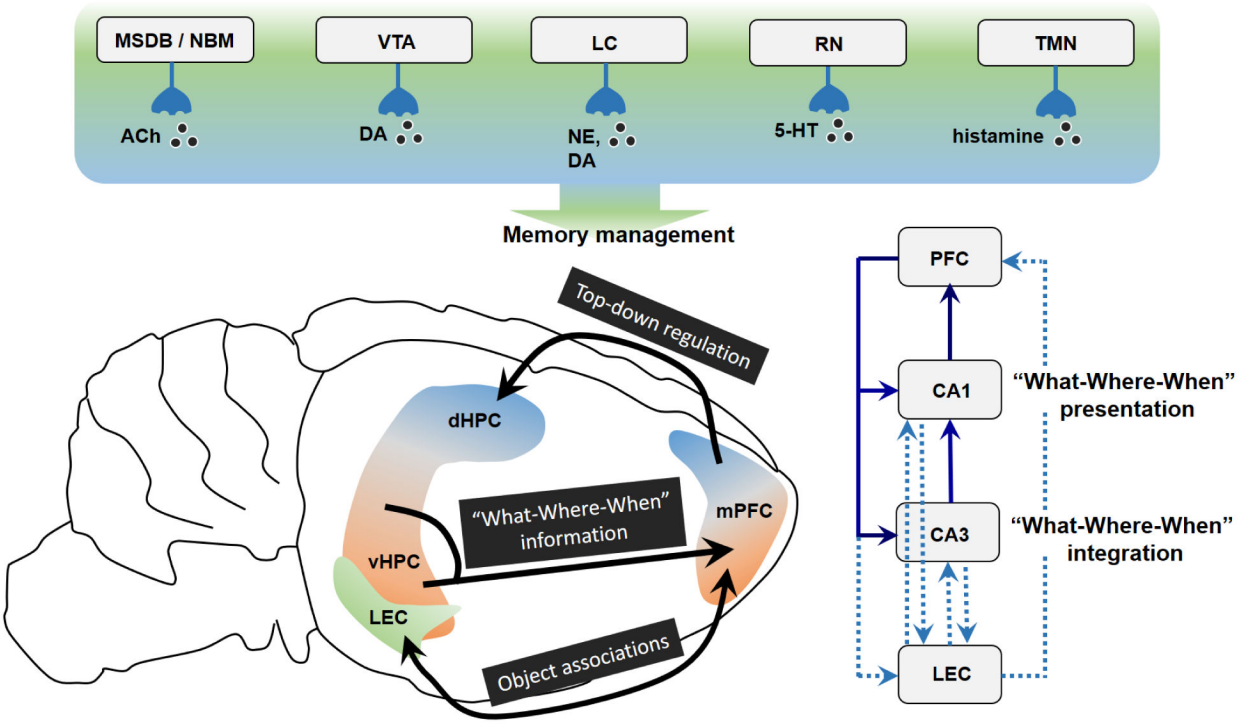

Figure 5.

A hypothetical system of episodic-like memory. The interaction between PFC and HPC underlies episodic-like memory, whereby the HPC conveys specific "What-Where-When" information unto the PFC that constantly regulates information selection. The indirect PFC-HPC pathway via LEC provides object-related, including contextual and temporal, details. Contrasting roles of CA1 and CA3 process the presentation or integration of "What-Where-When" representation, respectively. Different neurotransmitters, including ACh, DA, NE, 5-HT and histamine, modulate memories in a distinct but complementary manner. Left panel: Locations of mPFC, HPC and LEC in the mouse brain. Right-bottom panel: Black and dashed arrows demonstrate direct and indirect PFC-HPC pathways, respectively. mPFC: medial prefrontal cortex; dHPC: dorsal hippocampus; vHPC: ventral hippocampus; LEC: lateral entorhinal cortex; MSDB: medial septum and diagonal band of Broca; NBM: nucleus basalis magnocellularis; RN: raphe nucleus; VTA: ventral tegmental area; TMN: tuberomammillary nucleus; LC: locus coeruleus; ACh: acetylcholine; 5-HT: serotonin; DA: dopamine; NE: norepinephrine.

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Table 1.

Pharmacological studies investigating the role of neurotransmitter systems of medial prefrontal cortex in object exploration tests. Substances are infused into the medial prefrontal cortex.

Species and strain	Treatment	Test	Time of treatment	Sample trial	Retention	Findings	Reference
Pigmented male rats	CNQX, 2.5μg (AMPA/kainate-R antagonist)	NOP	Pre-sample	4min	3 h	No effect	Barker&Warburton, 2011a
Wistar male rats	AP5, 2.5μg (NMDA-R antagonist)	NOP	Post-sample	5min	3h	No effect	Akirav&Maroun, 2006
		NOP	Post-sample	5min	24h	Impaired	
Rats	MPEP, 1–10μg (mGlu5-R antagonist)	NOP	Pre-sample	5min	5min	Impaired 5 and 10μg	Christoffersen et al., 2008
ICR male mice	SCH23390, 1.0μg (DA D1/5-R antagonist)	NOP	Pre-sample	10min	1h	No effect	Nagai et al., 2007
		NOP	Pre-sample	10min	24h	Impaired	
Sprague-Dawley male rats	SCH23390 (DA D1/5-R antagonist)	NOP	Pre-sample	5min	5min	Impaired	Clausen et al., 2011
Sprague-Dawley male rats	SCH23390, 1.0μg (DA D1-R antagonist)	NOP	Pre-sample	15min	24h	Impaired	De Bundel et al., 2013
Dark Agouti male rats	SCH23390, 5mM/1.0μl (DA D1/5-R antagonist)	NOP	Pre-sample	4min	1h	No effect	Savalli et al., 2015
Wistar male rats	SCH23390, 1.5μg (DA D1/5-R antagonist)	NOP	Post-sample	5min	24h	Impaired	Rossato et al., 2013
		NOP	6 h post-sample	5min	24h	No effect	
Wistar male rats	SCH23390, 0.5–3.0μg (DA D1/5-R antagonist)	NOP	Post-sample	reach 20s	1h	Impaired 3.0 μg	Papp et al., 2017
Sprague-Dawley male rats	SKF81297, 0.03–3.0μg (DA D1/5-R agonist)	NOP	Pre-sample	2min	24h	Facilitated 0.03μg	De Bundel et al., 2013
Wistar male rats	SKF81297, 0.025–0.05μg (DA D1/5-R agonist)	NOP	Pre-sample	5min	10min	Impaired 0.05μg	Pezze et al., 2015
Wistar male rats	SKF81297, 0.05–0.75μg (DA D1-R agonist)	NOP	Post-sample	reach 20s	24h	Facilitated 0.2μg	Papp et al., 2017
ICR male mice	Raclopride, 5.0μg (DA D2-R antagonist)	NOP	Pre-sample	10min	1h	No effect	Nagai et al., 2007
		NOP	Pre-sample	10min	24h	No effect	

Species and strain	Treatment	Test	Time of treatment	Sample trial	Retention	Findings	Reference
Lister Hooded male rats	L741,626, 0.63–5.0μg (DA D2-R antagonist)	NOP	Pre-sample	3min	2min	Impaired	Watson et al., 2012
Wistar male rats	L741.626, 0.5–1.0μg (DA D2-R antagonist)	NOP	Post-sample	reach 20s	1h	Impaired 1.0 μg	Papp et al., 2017
Wistar male rats	Quinpirole, 3.0μg (DA D2-R agonist)	NOP	Post-sample	5min	24h	No effect	Rossato et al., 2013
Wistar male rats	Quinpirole, 0.1–5.0μg (DA D2-R agonist)	NOP	Post-sample	reach 20s	24h	Facilitated 1.0μg	Papp et al., 2017
Lister Hooded male rats	S33084, 0.63–2.5μg (DA D3-R antagonist)	NOP	Pre-sample	3min	4h	Facilitated	Watson et al., 2012
Wistar male rats	SB-277,011, 0.1–1.0μg (DA D3-R antagonist)	NOP	Post-sample	reach 20s	24h	Facilitated 0.5μg	Papp et al., 2017
Wistar male rats	7-OH-DPAT, 0.1–10μg (DA D3-R agonist)	NOP	Post-sample	reach 20s	1h	Impaired 10 μg	Papp et al., 2017
Wistar male rats	MDL11,939, 0.3μg (5-HT2A-R antagonist)	NOP	Pre-test	5min	3h	No effect	Bekinschtein et al., 2013
Wistar male rats	MDL11,939, 0.3μg (5-HT2A-R antagonist)	OPP	Pre-test	5min	3h	No effect	Bekinschtein et al., 2013
Lister Hooded male rats	MLA, 100nM (α7nACh-R antagonist)	OPP	Pre-sample	3min	24h	No effect	Sabec et al., 2018
Lister Hooded male rats	DHβE, 1μM (α4β2nACh-R antagonist)	OPP	Pre-test	3min	24h	No effect	Sabec et al., 2018
Pigmented male rats	CNQX, 2.5μg (AMPA/kainate-R antagonist)	TOM	Pre-sample2	4min	3h	Imapired	Barker&Warburton, 2011a
		TOM	Pre-test	4min	3h	Impaired	
Pigmented male rats	AP5, 5.0μg (NMDA-R antagonist)	TOM	Pre-sample2	4min	3h	Imapired	Barker&Warburton, 2011a
		TOM	Pre-test	4min	3h	No effect	
Wistar male rats	MDL11,939, 0.3μg (5-HT2A-R antagonist)	TOM	Pre-test	5min	3h	Impaired	Bekinschtein et al., 2013
Pigmented	Scopolamine, 10μg	TOM	Pre-sample2	4min	3h	Imapired	Barker&Warburton, 2011a

Species and strain	Treatment	Test	Time of treatment	Sample trial	Retention	Findings	Reference
male rats	(mAChR antagonist)	TOM	Pre-test	4min	3h	No effect	
Pigmented male rats	CNQX, 2.5μg (AMPA/kainate-R antagonist)	OiP	Pre-sample	5min	5min	Impaired	Barker&Warburton, 2008
Pigmented	AP5, 5.0μg	OiP	Pre-sample	5min	5min	Impaired	Barker&Warburton, 2008
male rats	(NMDA-R antagonist)	OiP	Pre-sample	5min	1h	Impaired	
		OiP	Pre-test	5min	1h	No effect	
Dark Agouti	SCH23390, 5mM/1.0μl	OiP	Pre-sample	5min	5min	Impaired	Savalli et al., 2015
male rats	(DA D1/5-R antagonist)	OiP	Pre-sample	5min	1h	Impaired	
		OiP	Pre-test	5min	1h	No effect	
Dark Agouti	SKF83566, 0.2mM/1.0μl	OiP	Pre-sample	5min	5min	Impaired	Savalli et al., 2015
male rats	(DA D1-R antagonist)	OiP	Pre-sample	5min	1h	Impaired	
Dark Agouti	Scopolamine, 10μg	OiP	Pre-sample	5min	5min	Impaired	Barker&Warburton, 2009
male rats	(mACh-R antagonist)	OiP	Pre-sample	5min	1h	Impaired	
		OiP	Pre-test	5min	1h	No effect	
Lister Hooded	MLA, 100nM	OiP	Pre-sample	5min	24h	Impaired	Sabec et al., 2018
male rats	(α7nACh-R antagonist)	OiP	Post-sample	5min	24h	No effect	
		OiP	Pre-test	5min	24h	No effect	
Lister Hooded	α-BGT, 1μM	OiP	Pre-sample	5min	24h	Impaired	Sabec et al., 2018
male rats	(α-nACh-R blocker)	OiP	Pre-test	5min	24h	No effect	
Lister Hooded	DHβE, 1μM	OiP	Pre-sample	5min	24h	No effect	Sabec et al., 2018
male rats	(α4β2nACh-R antagonist)	OiP	Post-sample	5min	24h	No effect	
		OiP	Pre-test	5min	24h	Impaired	

Abbreviations: AP5, 2-amino-5-phosphonopentanoic acid; MPEP, 2-methyl-6-(phenylethynyl)-pyridine; CNQX, 6-Cyano-7-nitroquinoxaline; MLA, methyllycaconitine citrate; α-BGT, α-bungarotoxin; DhβE, Dihydro-β-erythroidine hydrobromide; NOP, novel object preference; OPP, object place preference; TOM, temporal order memory; OiP, object-in-place; s, seconds; min, minutes; h, hours.

Table 2.

Lesions and inactivation studies on the entorhinal cortex in object exploration tests.

Species and strain	Treatment	Test	Time of treatment	Sample trial	Retention	Findings	Reference
Harlan Wistar male rats	NMDA lesions, whole EC	NOP 2 copies	Pre-sample	5min	2h	Impaired	Nyakas et al., 2009
Wistar male rats	Anisomycin, 160μg (protein synthesis inhibitor), EC	NOP 2 distinct	Post-sample	5min	3h	No effect	Lima et al., 2009
			Post-sample	5min	24h	Impaired	
			3h post-sample	5min	24h	No effect	
			6h post-sample	5min	24h	No effect	
Wistar male rats	Emetine, 50μg (protein synthesis inhibitor), EC	NOP 2 distinct	Post-sample	5min	3h	No effect	Lima et al., 2009
			Post-sample	5min	24h	Impaired	
			3h post-sample	5min	24h	No effect	
			6h post-sample	5min	24h	No effect	
Wistar male rats	Cycloheximide, 20μg (protein synthesis inhibitor), EC	NOP 2 distinct	Post-sample	5min	3h	No effect	Lima et al., 2009
			Post-sample	5min	24h	Impaired	
			3h post-sample	5min	24h	No effect	
			6h post-sample	5min	24h	No effect	
Long Evans male rats	Radio-frequency lesions, whole EC	SNOP 5 distinct	Pre-sample	4minx6	4min	Impaired SD m-Impaired NO	Parron&Save 2004
Long Evans male rats	Radio-frequency lesions, whole EC	SNOP 4 distinct	Pre-sample	4minx6	30s	Impaired SD	van Cauter et al., 2008a
					4&10min	Impaired SD	
					4&10min	No effect in NO	
Long Evans male rats	Radio-frequency lesions, LEC	NOP 2 copies	Pre-sample	reach 15s	2min	No effect	van Cauter et al., 2013
Lister Hooded male rats	Ibotenic acid lesions, LEC	NOP 2 copies	Pre-sample	3min or reach 15s	2min	No effect	Wilson et al., 2013b
Lister Hooded male rats	Ibotenic acid lesions, LEC	NOP 2 copies	Pre-sample	3min or reach 15s	2min	No effect	Wilson et al., 2013c
Lister Hooded male rats	Ibotenic acid lesions, LEC	NOP 2 copies	Pre-sample	3min or reach 15s	1min	No effect	Kuruvilla&Ainge, 2017
Long Evans	Ibotenic acid lesions,	NOP	Pre-sample	5minx3	3min	Impaired	Hunsaker et al., 2013

Species and strain	Treatment	Test	Time of treatment	Sample trial	Retention	Findings	Reference
male rats	LEC	3 distinct					
Lister Hooded male rats	Ibotenic acid lesions, LEC	NOP 4 distinct	Pre-sample	4minx6	1min	Impaired	Kuruvilla&Ainge, 2017
Lister Hooded male rats	Ibotenic acid lesions, LEC	OPP 2 copies	Pre-sample	3min or reach 15s	2min	No effect	Wilson et al., 2013c
Long Evans male rats	Radio-frequency lesions, LEC	OPP * 1 copy	Pre-sample	reach 15s	2min	No effect	van Cauter et al., 2013
Lister Hooded male rats	Ibotenic acid lesions, LEC	OLP ** 2 distinct	Pre-sample	3min or reach 15s	2min	Impaired	Wilson et al., 2013c
Long Evans male rats	LEC lesions	SNOP 3 distinct	Pre-sample	4minx6	4min	No effect in SD No effect in NO	Rodo et al., 2017
Long Evans male rats	Radio-frequency lesions, LEC	SNOP 4 distinct	Pre-sample	4minx6	4min	Impaired SD Imapired NO	van Cauter et al., 2013
Long Evans male rats	LEC lesions	SNOP 4 distinct	Pre-sample	4minx6	4min	No effect in SD Impaired NO	Rodo et al., 2017
Long Evans male rats	LEC lesions	SNOP 4 copies	Pre-sample	4minx6	4min	No effect in SD No effect in NO	Rodo et al., 2017
Long Evans male rats	Radio-frequency lesions, MEC	NOP 2 copies	Pre-sample	reach 15s	2min	No effect	van Cauter et al., 2013
Long Evans male rats	NMDA lesions, MEC	NOP 2 copies	Pre-sample	15min	3h	No effect	Hales et al., 2014
Lister Hooded male rats	Ibotenic acid lesions, MEC	NOP 2 copies	Pre-sample	3min or reach 15s	1min	No effect	Kuruvilla&Ainge, 2017
Long Evans male rats	NMDA lesions, MEC	NOP 2 copies	Post-sample	15minx4	2w	No effect	Hales et al., 2018
Sim1 cre mice	AAV-Flex-TeLC MEC	NOP 2 copies	Pre-sample	5min	3min	No effect	Tennant et al., 2018
Long Evans male rats	Ibotenic acid lesions, MEC	NOP 3 distinct	Pre-sample	5minx3	3min	No effect	Hunsaker et al., 2013
Lister Hooded	Ibotenic acid lesions,	NOP	Pre-sample	4minx6	1min	No effect	Kuruvilla&Ainge, 2017

Species and strain	Treatment	Test	Time of treatment	Sample trial	Retention	Findings	Reference
male rats	MEC	4 distinct					
Long Evans male rats	NMDA lesions, MEC	OPP 2 copies	Pre-sample	15min	3h	No effect	Hales et al., 2014
Sim1 cre mice	AAV-Flex-TeLC MEC	OPP 2 copies	Pre-sample	5min	3min	Impaired	Tennant et al., 2018
Long Evans male rats	Radio-frequency lesions, MEC	OPP * 1 copy	Pre-sample	reach 15s	2min	Imapired	van Cauter et al., 2013
Long Evans male rats	MEC lesions	SNOP 3 distinct	Pre-sample	4minx6	4min	Impaired SD No effect in NO	Rodo et al., 2017
Long Evans male rats	Radio-frequency lesions, MEC	SNOP 4 distinct	Pre-sample	4minx6	4min	Impaired SD No effect in NO	van Cauter et al., 2013
Long Evans male rats	MEC lesions	SNOP 4 distinct	Pre-sample	4minx6	4min	Impaired SD No effect in NO	Rodo et al., 2017
Long Evans male rats	MEC lesions	SNOP 4 copies	Pre-sample	4minx6	4min	No effect in SD No effect in NO	Rodo et al., 2017

Abbreviations: EC: entorhinal cortex; LEC: lateral entorhinal cortex; MEC: medial entorhinal cortex; TeLC, tetanus toxin light chain; SD, spatial displaced object; NO, novel object; m-Impaired, moderately impaired; s, seconds; min, minutes; h, hours; w, weeks.

*one object was located, followed by two identical objects of the explored type.

**two distinct objects were located, followed by two identical objects chosen form either the explored type.

Table 3.

Findings of the novel object preference test based on lesions and inactivation (lidocaine & GABAa receptors ago- and antagonists) studies in the hippocampus (unless specified, the target region is dorsal hippocampus).

Species and strain	Treatment	Apparatus	Time of treatment	Sample trial	Retention	Findings	Reference
Long Evans	Radio-frequency	OF	Pre-sample	reach 30s	10s or 1min	No effect	Clark et al., 2000
male rats	lesions, whole HPC		Pre-sample	reach 30s	10min or 1h	Impaired	
			Pre-sample	reach 30s	24h	No effect	
Long Evans	Ibotenic acid lesions,	OF	Pre-sample	reach 30s	10s or 1min	No effect	Clark et al., 2000
male rats	whole HPC		Pre-sample	reach 30s	10min or 1h	Impaired	
			Pre-sample	reach 30s	24h	m-Impaired	
Long Evans	NMDA lesions,	OF	Pre-sample	5min	15min	No effect	Gaskin et al., 2003
male rats	whole HPC		Pre-sample	5min	24h	No effect	
Long Evans	Ibotenic acid lesions,	OF					Broadbent et al., 2004
male rats	~50–75% HPC		Pre-sample	15min	3h	No effect	
	~ventral 50% HPC		Pre-sample	15min	3h	No effect	
	whole HPC		Pre-sample	15min	3h	Impaired	
Lister Hooded	Ibotenic acid lesions,	Y-maze	Pre-sample	reach 25s	<30s	No effect	Winters et al., 2004
male rats	whole HPC		Pre-sample	or 5 min	15min	No effect	
			Pre-sample		1h	No effect	
			Pre-sample		24h	No effect	
Lister Hooded	Ibotenic acid lesions,	Y-maze	Pre-sample	reach 25s	15min, 1h,	No effect	Forwood et al., 2005
male rats	whole HPC			or 3min	24h & 48h		
Long Evans	NMDA lesions,	OF	Pre-sample	5minx5	24h	No effect	Mumby et al., 2005
male rats	whole HPC		Pre-sample	5minx5	1w	No effect	
			Pre-sample	5minx5	3w	No effect	
Lister Hooded	ibotenic acid lesions,	OF	Pre-sample	reach 30s	10s or 1min	No effect	Ainge et al., 2006
male rats	~60% HPC		Pre-sample	reach 30s	10min or 1h	Impaired	
			Pre-sample	reach 30s	24h	Impaired	
Lister Hooded	ibotenic acid lesions,	OF	Pre-sample	reach 30s	10s or 1min	No effect	Ainge et al., 2006
male rats	whole HPC		Pre-sample	reach 30s	10min or 1h	No effect	
			Pre-sample	reach 30s	24h	Impaired	

Species and strain	Treatment	Apparatus	Time of treatment	Sample trial	Retention	Findings	Reference
PV cre	Lenti-EF1a-DIO-hM3Dq	OF	Pre-sample	10min	1h	No effect	Zou et al., 2016
male mice	dorsal dentate gyrus		Pre-sample	10min	24h	No effect	
C57BL/6J	AAV-CaMKIIa-hM4Di	OF	Pre-sample	reach 30s	24h	No effect	Tuscher et al., 2018
female OCT	AAV-CaMKIIa-hM4Di		Post-sample	reach 30s	24h	No effect	
mice	AAV-CaMKIIa-KORD		Post-sample	reach 30s	24h	Impaired	
GAD-65 cre	AAV-CAG-DIO-hM3Dq	OF	Post-sample	10min	24h	No effect	Yu et al., 2018
male mice							
C57BL/6N	VGAT-cre +	OF	Post-sample	10min	24h	No effect	Yu et al., 2018
male mice	AAV-EF1a-DIO-hM4Di						

Abbreviations: OF: open field; CT maze, circular track maze; BT maze, bow-tie shaped maze; OCT: ovariectomized; m-Impaired: moderately impaired; s, seconds; min, minutes; h, hours; w, weeks.

** objects were presented one by one;

in a less-habituated context.

AAV and lentiviral vectors carrying excitatory or inhibited receptors are transferred into the dorsal hippocampal neurons and can be activated by clozapine-*N*-oxide (hM3Di & hM4Dq) and salvinorin B (KORD) at the selected time.

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Table 4.

Pharmacological studies investigating the role of neurotransmitter systems in the hippocampus in object exploration tests. Substances are infused into the dorsal hippocampus, primarily the CA1 area.

Species and strain	Treatment	Test	Time of treatment	Sample trial	Retention	Findings	Reference
Rats	NBQX	NOP	Pre-test	5minx5	24h	Impaired	Iwamura et al., 2016
	(AMPA-R antagonist)	NOP	Pre-test	5minx5	1w	Impaired	
		NOP	Pre-test	5minx5	3w	Impaired	
Long-Evans	AP5, 3.75μg	NOP	Pre-sample	1min	5min	No effect	Baker&Kim, 2002
male rats	(NMDA-R antagonist)	NOP	Pre-sample	1min	3h	Impaired	
Pigmented	AP5, 25mM/0.5μl	NOP	Pre-sample	4min	1h	No effect	Barker&Warburton, 2015
male rats	(NMDA-R antagonist)						
Long Evans	AP5, 40mM/1.0μl	NOP	Pre-sample	5min	5min	No effect	Sugita et al., 2015
male rats	(NMDA-R antagonist)	NOP	Pre-sample	5min	5min	Impaired/4obj	
Wistar	AP5, 20–40mM	NOP	Pre-sample	3min	20min	No effect	Yamada et al., 2017
male rats	(NMDA-R antagonist)						
Rats	AP5	NOP	Pre-test	5minx2	24h	No effect	Iwamura et al., 2016
	(NMDA-R antagonist)	NOP	Pre-test	5minx2	1w	Impaired	
Rats	AP5	NOP	Pre-test	5minx5	1w	No effect	Iwamura et al., 2016
	(NMDA-R antagonist)	NOP	Pre-test	5minx5	3w	Impaired	
Wistar	SCH23390, 2.0μg	NOP	Pre-sample	5min	90min	No effect	Balderas et al., 2013
male rats	(DA D1/5-R antagonist)	NOP	Pre-sample	5min	24h	No effect	
Sprague-Dawley	SCH23390, 1.0μg	NOP	Pre-sample	15min	24h	Impaired	De Bundel et al., 2013
male rats	(DA D1/5-R antagonist)						
Wistar	SCH23390, 1.5μg	NOP	Post-sample	5min	24h	No effect	Rossato et al., 2013
male rats	(DA D1/5-R antagonist)	NOP	6 h post-sample	5min	24h	No effect	
Wistar	SCH23390	NOP	Post-sample	5min	24h	Impaired	Furini et al., 2014
male rats	(DA D1/5-R antagonist)	NOP	1h post-sample	5min	24h	Impaired	
		NOP	3h post-sample	5min	24h	No effect	
Wistar	SCH23390, 1.5μg	NOP	Post-sample	5 min	24h	No effect	Rossato et al., 2015
male rats	(DA D1/5-R antagonist)	NOP	6 h post-sample	5 min	24h	No effect	
		NOP	Pre-test	5 min	24h	No effect	

Species and strain	Treatment	Test	Time of treatment	Sample trial	Retention	Findings	Reference
Wistar male rats	SCH23390, 0.5–3.0μg (DA D1/5-R antagonist)	NOP	Post-sample	reach 20s	1h	Impaired 3.0 μg	Papp et al., 2017
Wistar male rats	SKF38393, 12.5μg (DA D1-R agonist)	NOP	Pre-sample	3min	90min	No effect	Balderas et al., 2013
		NOP	Pre-sample	3min	24h	No effect	
Sprague-Dawley male rats	SKF81297, 0.03–3.0μg (DA D1/5-R agonist)	NOP	Pre-sample	2min	24h	Facilitated	De Bundel et al., 2013
Wistar male rats	SKF81297, 0.05–0.5μg (DA D1/5-R agonist)	NOP	Post-sample	reach 20s	24h	Facilitated 0.5μg	Papp et al., 2017
Wistar male rats	L741.626, 0.5–2.5μg (DA D2-R antagonist)	NOP	Post-sample	reach 20s	1h	No effect	Papp et al., 2017
Wistar male rats	Quinpirole, 3.0μg (DA D2-R agonist)	NOP	Post-sample	5min	24h	No effect	Rossato et al., 2013
Wistar male rats	Quinpirole, 0.1–5.0μg (DA D2-R agonist)	NOP	Post-sample	reach 20s	24h	Facilitated 5.0μg	Papp et al., 2017
Wistar male rats	SB-277,011, 0.1–1.0μg (DA D3-R antagonist)	NOP	Post-sample	reach 20s	24h	Facilitated 1.0μg	Papp et al., 2017
Wistar male rats	7-OH-DPAT, 0.1–10μg (DA D3-R agonist)	NOP	Post-sample	reach 20s	1h	Impaired 0.1–1.0μg	Papp et al., 2017
C57BL/6J male mice	TCB-2, 1μg (5-HT2A-R agonist)	NOP	Post-sample	10min	24h	Facilitated	Zhang et al., 2016
Wistar male rats	Scopolamine, 30μg (mACh-R antagonist)	NOP	Post-sample	10min	90min	Impaired	Balderas et al., 2012
		NOP	Post-sample	10min	24h	No effect	
		NOP	160min post-sample	10min	24h	No effect	
		NOP	90min pre-test	10min	24h	No effect	
Long-Evans male rats	Nicotine, 0.5–2μg (nACh-R agonist)	NOP	Pre-sample	3 min or reach 25s	72h	Facilitated 0.5–1.0μg	Melichercik et al., 2012
Wistar male rats	Pyrilamine, 50mM/1.0μl (H1-R antagonist)	NOP	Post-sample	5min	24h	No effect	de Silveira et al., 2013
		NOP	30min post-sample	5min	24h	Impaired	
		NOP	2h post-sample	5min	24h	Impaired	
		NOP	6 h post-sample	5min	24h	No effect	

Species and strain	Treatment	Test	Time of treatment	Sample trial	Retention	Findings	Reference
Wistar	Pyridylethylamine,	NOP	Post-sample	5min	24h	No effect	de Silveira et al., 2013
male rats	10mM/1.0µl	NOP	30min post-sample	5min	24h	No effect	
	(H1-R agonist)	NOP	2h post-sample	5min	24h	No effect	
		NOP	6 h post-sample	5min	24h	No effect	
Wistar	Ranitidine, 50mM/1.0µl	NOP	Post-sample	5min	24h	No effect	de Silveira et al., 2013
male rats	(H2-R antagonist)	NOP	30min post-sample	5min	24h	Impaired	
		NOP	2h post-sample	5min	24h	Impaired	
		NOP	6 h post-sample	5min	24h	No effect	
Wistar	Dimaprit, 10mM/1.0µl	NOP	Post-sample	5min	24h	No effect	de Silveira et al., 2013
male rats	(H2-R agonist)	NOP	30min post-sample	5min	24h	No effect	
		NOP	2h post-sample	5min	24h	No effect	
		NOP	6 h post-sample	5min	24h	No effect	
Wistar	Thioperamide,	NOP	Post-sample	5min	24h	No effect	de Silveira et al., 2013
male rats	50mM/1.0µl	NOP	30min post-sample	5min	24h	No effect	
	(H3-R antagonist)	NOP	2h post-sample	5min	24h	No effect	
		NOP	6 h post-sample	5min	24h	No effect	
Wistar	Imetit, 10mM/1.0µl	NOP	Post-sample	5min	24h	No effect	de Silveira et al., 2013
male rats	(H3-R agonist)	NOP	30min post-sample	5min	24h	Impaired	
		NOP	2h post-sample	5min	24h	Impaired	
		NOP	6 h post-sample	5min	24h	No effect	
Wistar	Timolol, 1µg	NOP	Post-sample	5min	24h	Impaired	Furini et al., 2010
male rats	(β-adrenergic antagonist)						
Wistar	Timolol, 1µg	NOP	Post-sample	5min	24h	Impaired	Mello-Carpes&Izquierdo, 2013
male rats	(β-adrenergic antagonist)						
Wistar	Timolol, 1µg	NOP	Post-sample	5min	24h	Impaired	Mello-Carpes et al., 2016
male rats	(β-adrenergic antagonist)						
Wistar	Norepinephrine, 1µg	NOP	Post-sample	5min	24h	No effect	Mello-Carpes&Izquierdo, 2013
male rats							
Wistar	Norepinephrine, 1µg	NOP	Post-sample	5min	24h	No effect	Mello-Carpes et al., 2016
male rats		NOP	Post-sample	5min	3w	Facilitated	
Wistar	WIN55,212–2, 1–2.0µg	NOP	Pre-sample	3min	20min	No effect	Suenaga&Ichitani, 2008

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Species and strain	Treatment	Test	Time of treatment	Sample trial	Retention	Findings	Reference
male rats	(cannabinoid-R agonist)						
Long-Evans	Apomorphine, 10–15μg	SNOP	Post-sample*	6min	3min	Impaired	Vago&Kesner, 2008
male rats	(DA D1/2-R agonist)					SD	
NMRI	RS23597, 0.016μg	SNOP	Post-sample*	6minx3	24h	Impaired	Nasehi et al., 2017
male mice	(5-HT4-R antagonist)					SD	
NMRI	RS67333, 0.016μg	SNOP	Post-sample*	6minx3	24h	Impaired	Nasehi et al., 2017
male mice	(5-HT4-R agonist)					SD	
Long-Evans	Scopolamine, 30μM/0.4μl	SNOP	Post-sample*	6min	3min	Impaired	Hunsaker et al., 2007b
male rats	(mACh-R antagonist)		CA3			SD and NO	
Long-Evans	Physostigmine, 30μM/0.4μl	SNOP	Post-sample*	6min	3min	Facilitated	Hunsaker et al., 2007b
male rats	(ACh-esterase inhibitor)		CA3			SD and NO	
NMRI	AM251, 0.2μg	SNOP	Post-sample*	6minx3	24h	Faciliated	Nasehi et al., 2017
male mice	(CB1-R antagonist)					SD	
Pigmented	AP5, 25mM/0.5μl	OiP	Pre-sample	5min	5min	Impaired	Barker&Warburton, 2015
male rats	(NMDA-R antagonist)	OiP	Pre-sample	5min	1h	Impaired	
		OiP	Pre-test	5min	1h	No effect	
Dark Agouti	SCH23390, 5mM/1.0μl	OiP	Pre-sample	5min	5min	No effect	Savalli et al., 2015
male rats	(DA D1/5-R antagonist)	OiP	Pre-sample	5min	1h	No effect	

Abbreviations: AP5, 2-amino-5-phosphonopentanoic acid; NBQX, 2,3-Dioxo-6-nitro-1,2,3,4-tetrahydrobenzo[f]quinoxaline-7-sulfonamide; PLL, palmitoylethanolamide; H-R: histamine receptors; CB-R: cannabinoid receptors; ECB, endocannabinoid; NOP, novel object preference; OPP, object place preference; SNOP, spatial and non-spatial object preference; OiP, object-in-place preference; obj, objects; SD, spatial displaced object; NO, novel object; s, seconds; min, minutes; h, hours; w, weeks.

*After the infusions, one more sample trial was given before the test trials of SNOP paradigm.

Table 5.

Lesion or inactivation studies performed with various episodic-like memory tests. ELM2–2 test: assesses episodic-like memory with 2 types of object, each type presented at different time points, and in the test trial one of the objects from each type is displaced to a new location (2 types of objects and 2 displaced ones). ELM2–1 test: assesses episodic-like memory with 2 types of object, each type presented at different time points, and in the test trial one of the recent familiar objects is displaced (2 types of objects and 1 displaced one). ELM4–2 test: assesses episodic-like memory with 4 distinct objects, 2 as a group presented at different time points, and in the test trial 2 out of 4 objects are displaced (4 different objects and 2 displaced ones).

				Findings in ELM 2–2 test				**Additional tests:**			
Animal	**Sex**	**Treatment**	**Region**	***Where***	***When***	***Interaction***	**Delay**	**NOP**	**OPP**	**TOM**	**Ref.**
Wistar	Male	Electrolytic lesions	CA3	P	P	Impair	1 h	P	P*	P	Li&Chao 2008
Wistar	Male	Infusion of muscimol before sample	CA1	Impair	Impair	Impair	1 h	(	not tested	)	Drieskens, 2017
Wistar	Male	NMDA lesions	PFC+CA3 disconnection	Impair	Impair	Impair	1 h	P	P	P	de Souza Silva et al., 2016
Wistar	Male	NMDA lesions	PFC+CA1 disconnection	P	P	Impair	1 h	P	Impair	P	Chao et al., 2017
Wistar	Male	NMDA lesions	PFC+LEC disconnection	P**	P	Impair	1 h	P	P	P	Chao et al., 2016
				Findings in ELM 2–1 test				**Additional tests:**			
Animal	**Sex**	**Treatment**	**Region**	***Where***	***When***	***What***	**Delay**	**NOP**	**OPP**	**TOM**	**Ref.**
Wistar	Male	Infusion of Muscimol before sample	DG/CA3	Impair	P	(not tested)	24 h	(	not tested	)	Barbosa 2012
Wistar	Male	Infusion of Muscimol before sample	CA1	Impair	Impair	(not tested)	24 h	(	not tested	)	Barbosa 2012
C57BL	Male	NMDA lesions	PFC	Impair	P	P	50 min	(	not tested	)	DeVito 2010
C57BL	Male	NMDA lesions	HPC	Impair	Impair	Impair	50 min	(	not tested	)	DeVito 2010
				Findings in ELM 4–2 test				**Additional tests:**			
Animal	**Sex**	**Treatment**	**Region**	***Where***	***When***	**Delay**	**OiP**	**NOP**	**OPP**	**TOM**	**Ref.**
Lister Hooded	Male	Infusion of NBQX before test	PFC-HPC disconnection	Impair	Impair	1 h	(	not	testing	)	Barker et al 2017

Lister Hooded	Male	Infusion of Daun02	pdCA1->PFC inactivation	P	Impair	1 h	P	P	P	Impair	Barker et al 2017
Lister Hooded	Male	Infusion of Daun02	iCA1->PFC inactivation	Impair	P	1 h	Impair	P	P	P	Barker et al 2017

NOP: novel object preference test; OPP: object place preference test; TOM: temporal order memory test; OiP: object-in-place test. P: presence of the test.

*spatial recognition was tested by the preference of time spent on explored location versus unexplored one in a radial-arm maze.

**the disconnected PFC-LEC group showed positive, but reduced, values of the *where* index.