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Short Communication

Time decay of object, place and temporal order memory in a paradigm assessing simultaneously episodic-like memory components in mice

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HIGHLIGHTS

- Mice successfully performed the three-trial object recognition task up to 2 h ITI.
- The different components of episodic-like memory display a similar time course decay.
- This paradigm may provide a usefulness tool for the screening of promnesic drugs.

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ABSTRACT

A common trait of numerous memory disorders is the impairment of episodic memory. Episodic memory is a delay-dependant memory, especially associating three components, the "what", "where" and "when" of a unique event. To investigate underlying mechanisms of such memory, several tests, mainly based on object exploration behaviour, have been set up in rodents. Recently, a three-trial object recognition task has been proposed to evaluate simultaneously the different components of episodic-like memory in rodents. However, to date, the time course of each memory component in this paradigm is not known. We characterised here the time course of memory decay in adult mice during the three-trial object recognition task, with inter-trial interval (ITI) ranging from 1 h to 4 h. We found that, with 1 h and 2 h, but not 4 h ITI, mice spent more time to explore the displaced "old object" relative to the displaced "recent object", reflecting memory for "what and when". Concomitantly, animals exhibited more exploration time for the displaced "old object" relative to the stationary "old object", reflecting memory for "what and where". These results provide strong evidence that mice establish an integrated memory for unique experience consisting of the "what", "where" and "when" that can persist until 2 h ITI.

1. Introduction

Episodic memory is one form of declarative memory that is early impaired in Alzheimer disease [1]. It is defined as the ability of recollecting the three components of a unique personal experience: "what" happened, "where" and "when" it occurred [2–4]. It also requires autonoetic consciousness (*i.e.* conscious experience of recollection) and involves mental time travel. As non-linguistic behavioural markers of autonoetics consciousness are missing, it is difficult to bring evidence of such capacity in non-human animals. To solve this issue, behavioural paradigms were described to test this memory in animal models, which is referred to as *episodic-like memory* (ELM, [5]) and based on the "what", "where" and "when" content of a unique episode. Clayton and Dickinson were the first to demonstrate ELM in animals. Indeed, they have shown that food-caching scrub jays are able to remember what kind of food was hidden, its location, and for how long they have stored it [5]. Otherwise, such a kind of memory has thereafter been reported in different animals species, for instance in meadow voles [6], great apes [7] and very recently in an invertebrate animal species, the common cuttlefish [8].

As rodents are the most used laboratory animals, several procedures have been described in those species. In rats, Babb and

Abbreviations: ELM, episodic-like memory; ITI, inter-trial interval; O_s, stationary old object; O_d, displaced old object; R_s, stationary recent object; R_d, displaced recent object.

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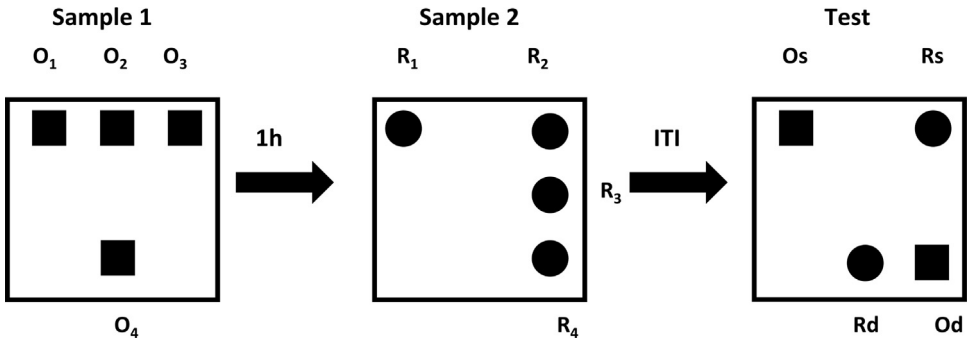

Fig. 1. Schematic representation of the simultaneous assessment of object, place and temporal order memory in mice. O_d: displaced old object, O_s: stationary old object, R_d: displaced recent object, R_s: stationary recent object, ITI: inter trial interval.

Crystal have adapted a food-rewarded memory test in an 8-arm radial-maze. Their findings revealed that a trained rat was able to remember what, where and when a preferred food item was previously encountered [9,10]. Ergorul and Eichenbaum [11] developed a novel approach in rats, based on a combination of odours (what) presented in different places (where) and in a specific order (when). In this experiment, rats need to use a combination of spatial "where" and olfactory "what" cues to distinguish "when" the event occurred. However, most of these procedures in rodents have never successfully demonstrated an integrated memory for "what", "where" and "when" components of the ELM without undergoing extensive training and food deprivation. In this respect, some studies have focused on a spontaneous behaviour of rodents: the innate tendency of rodents to seek novelty. These experiments are based on the so-called object recognition paradigm that has been reported in several studies [12–14], including ours [15]. Such procedure does not involve extensive training and rule learning. This widely used task allows to assess the different components of ELM in separate paradigms: (a) object recognition memory [12,16,17]; (b) object location memory [16,17] and (c) temporal order memory [18,19]. More recently, new protocols assessing simultaneously the three components of ELM into a single object recognition paradigm, have been introduced in order to model more closely human episodic memory [13,14,20–22]. Protocols differ somewhat between rats and mice: *e.g.* duration of familiarisation [13,14,23], shape of the open field [13,14,23], computed ratios to evaluate memory performance [13,14,22,24–26], objects configuration across the sessions [13,14,23,24]. In the present study, we used the protocol initially designed by Kart-Teke et al. [20,21] in rats, that was applied in mice in only one study conducted by Dere et al. [24]. In this paradigm, animals are exposed at the same time to old stationary and displaced objects together with recent stationary and displaced objects, which allows the assessment of both recency and spatial arrangement of objects. ELM performances are also highly dependent on the duration of the inter-trial interval (ITI) [16]. In above studies, for both mice [13,14,24,25] and rats [20,21], the most frequently used ITI was around 1 h, except for previous work undertaken in rat in which object recognition memory was tested at 6 h and up to 23 h [26] or at 24 h [23]. To date, in mice the time course of memory decay of object, place and temporal order have not been yet characterised in the paradigm assessing simultaneously the three components of ELM. Therefore, using a simple statistical method of data analysis that takes into account the inseparable link between the "what", "where" and "when" information, we characterised here the time-course of the memory trace decay of object, of its place and its temporal order of appearance in the three-trial object recognition task. The three components of ELM have been assessed in mice with inter-trial intervals ranging from 1 h to 4 h.

2. Materials and methods

2.1. Animals

All experiments were carried out in adult male NMRI mice (12 weeks old, purchased from Janvier labs, France), housed in standard polycarbonate cages, maintained on a reversed 12 h light-dark cycle (20:00–8:00), at constant temperature (21 °C) and humidity (55%). Water and food were available *ad libitum*. Three groups of 10–12 animals were used, one for each ITI tested (1 h, 2 h or 4 h). All experiments were in accordance with the European Community's Council Directive and approved by the regional ethics committee (Comité d'Ethique NOrmandie en Matière d'EXpérimentation Animale, CENOMEXA, agreement number: 03-08-11/16/08-14).

2.2. Apparatus and objects

The object recognition test was conducted in a black painted open box (32 cm × 32 cm × 20 cm) made of polyvinyl chloride, with a light intensity around 10 lx at the centre. Two types of objects (in quadruplicate) made of plastic were presented (Playmobil® figurine *versus* assembly Lego®). The objects used in the present study were previously tested in our laboratory to check for absence of innate preference of the mice for one of this pair (*data not shown*). The objects were placed 5 cm away from the walls and fixed by Patafix® on the box floor to avoid their displacement by mice. After each session, the box and the objects were cleaned with diluted ethanol (70%) and dried to prevent any residual olfactory cues.

2.3. Behavioural procedure

Testing occurred during the dark phase of the animal's cycle. The mice were placed in the experimental room 30 min before the beginning of the experiments.

The test procedure consisted in four sessions: familiarisation, sample 1, sample 2 and test session.

Animals were familiarised to the open field (2 × 3 min per day) for three consecutive days. On the first day, mice were placed (per three) in the empty open field. On the second day, they were placed individually. On the third day, the mouse was allowed to explore freely the apparatus in the presence of an object placed at the centre of the open field, different from those used during the following sessions. The object recognition task began on day 4 (Fig. 1), during which the "what", "where" and "when" components of ELM were combined into a single exploration task according to the procedure described in rats by Kart-Teke et al. [20,21], and in mice by Dere et al. [24]. The animals received two sample sessions, spaced by 1 h, followed by one test session after a given ITI (1 h, 2 h or 4 h). In sample 1 (5 min), the mouse was placed in the open field containing 4