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A novel experimental approach to episodic memory in humans based on the privileged access of odors to memories.

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Abbreviations

CR: Correct Rejection;

FA: False Alarm;

WWW: An accurate recall of both the location and the context associated with a target odor;

WWhere: An accurate recall of the location but not the context associated with a target odor;

WWhich: An accurate recall of the context but not the location associated with a target odor;

What: An inaccurate recall of both the location and the context associated with a target odor.

Abstract

Episodic memory is defined as the conscious recollection of a personal event (*What*) in its spatial (*Where*) and contextual (*Which context*) environment. In existing approaches, human episodic memory is either explored separately from real-life situations or is not fully controlled. In this study, we propose an intermediate approach, inspired by animal studies, that permits the control of the encoding and recall phases, while still being ecologically valid. As odors are known to be especially evocative reminders, we explored the memory of olfactory episodes. During trial-unique encoding, participants freely explored three episodes, one episode per day, each composed of three unnamable odors (*What*) that were positioned at specific locations on a board (*Where*) within a visual context (*Which context*). On the fourth day, both old and new odors were presented, and when an odor was recognized, the participants had to remember both its spatial location and the visual context in which it occurred. In Experiment 1, the participants were highly proficient at recognizing odors, and they recall the spatio-contextual environment associated with these odors in approximately half of the trials. To adapt the recall procedure to the constraints of fMRI, we conducted Experiment 2 demonstrating that trial repetition did not disturb the memory process. Thus, we first validated our protocol, which investigates the memory of olfactory episodes in a fully controlled way that is as close as possible to real-life situations. Then, we demonstrated the adaptability of our protocol for the future exploration of the neural networks implicated in episodic recall.

Keywords: Human episodic memory; Spatio-contextual memory; Odor recognition memory; Ecological approach; Laboratory-based approach; Proust phenomenon.

1 Introduction

Episodic memory was first characterized as the vivid and conscious recollection of a unique personal event and of the spatial and temporal contexts in which it occurred (Tulving, 1972). Thus, episodic memory was defined on the basis of different types of stored information: *What* happened, *Where* and *When*. Recently, Easton and Eacott (Eacott and Easton, 2010; 2008) pointed out that humans have difficulty remembering the date or the temporal order of episodic events (Friedman, 2007). Because the temporal dimension of such events is often deduced from context (e.g., "It was snowing and I had this haircut, so it must have been Christmas, three years ago"), the authors noted that episodic memory is more of a "snapshot" of an episode, in which time forms a part of the context but is not essential. As a consequence, these authors defined episodic memory in terms of the dimensions "*What*, *Where*, and *Which occasion* or *Which context*," rather than in terms of "*What*, *Where*, and *When*."

To study the retrieval of past events, two approaches are typically used: *ecological* and *laboratory-based* approaches. In the *ecological* approach, experimenters test autobiographical memory by interrogating participants about real-life memories encoded in their past (e.g., Fink et al., 1996; Janata, 2009; Levine et al., 2004; Nadel et al., 2007; Piolino et al., 2004). The participants must relate memories evoked by a cue (e.g., photographs, faces, sentences, or music), an approach that is quite ecological, as it is close to the conditions under which real-life recall typically occurs. However, experimenters cannot control the veracity of the recalled events. In the *laboratory-based* approach, experimenters test the memorization of artificial episodes created in the laboratory using recognition tasks (e.g., Daselaar et al., 2003; Donaldson et al., 2010; Konishi et al., 2000; Watanabe et al., 2008). The participants study a list of items (e.g., pictures, words, sounds, or odors) and, at a later point, must distinguish between these 'old' items (targets) and 'new' items (distractors). This method controls for the encoding conditions, the retention time and the veracity of the retrieval. However, the to-be-remembered information is often one-dimensional (*What*) and is therefore poor

in comparison with a real-life episode. McDermott et al. (2009) have underscored the interest to propose a new approach to the study and understanding of human episodic memory, one that should be halfway between these two methods and should retain the respective advantages of each. Toward this end, we developed a laboratory-based method to investigate episodic memory that is as ecologically valid as possible but in which encoding, retention delay and retrieval are fully controlled.

In our approach, the to-be-remembered episodes are unique, rich, close-to-real-life episodes, and in agreement with the definitions of episodic memory proposed by Tulving (1972) and Easton and Eacott (Eacott and Easton, 2010; 2008). The episodes were composed of three dimensions: odors (*What*) positioned at specific locations on a board (*Where*) and presented in a visual context (i.e., a picture of a landscape, *Which context*). During the encoding phase, the participants freely explored the episodes. After consolidation, episodic memories were explored using simple recognition and retrieval tasks, ensuring the evaluation of the memory content accuracy. This protocol did not address the conscious re-experience of past events, and therefore investigate what Clayton and colleagues referred to as episodic-like memory (Clayton et al., 2001; Easton and Eacott, 2008).

We used odors as cues for two reasons. First, among all types of stimuli, odors are known to be especially evocative reminders, the best illustration of this phenomenon being the Proust's Madeleine story (Proust, 1913). Experimental studies have later shown that odor-evoked memories are more emotional, more associated with subjective experience, and more vivid than those recalled by other sensory cues (Goddard et al., 2005; Herz, 2004; Herz and Cupchik, 1995; Herz et al., 2004; Larsson and Willander, 2009; Miles and Berntsen, 2011). This strong connection between olfaction, emotion and memory makes olfaction a privileged sense for accessing memories. Additionally, because odors are highly difficult to identify (Jonsson and Olsson, 2003; Lawless and Engen, 1977), participants favor perceptual cues to encode them and thereby limit the use of verbal processes. The use of odors thus allows us to specifically explore episodic, but not semantic, memory.

The aims of the current study were twofold. First, we wanted to validate our novel paradigm designed for the study of episodic memory, and second, we wanted to test the adaptability of this procedure to the constraints of functional Magnetic Resonance Imaging (fMRI). Experiment 1 evaluated the recognition of non-familiar odors and the retrieval of spatio-contextual environments associated with these odors. Experiment 2 addressed the effects of trial repetition on memory scores, which was necessary to adapt the recall procedure to fMRI constraints.

2 **Experiment 1**

2.1 Objective and design

Experiment 1 was principally designed to validate our methodological approach for the study of episodic memory. This behavioral validation consisted of an evaluation of participants' abilities to freely encode unique rich episodes and to later recall these episodes during odor recognition and episodic retrieval tasks.

2.2 Materials and Methods

2.2.1 Participants

Twenty-two healthy participants [14 women; age: 22.6 ± 7.9 (mean ± standard deviation)] consented to participate in the experiment. These participants were recruited by means of posters or electronic mail on campus and received 20 euros in compensation. The participants reported normal senses of smell and no visual impairments. The study was conducted in accordance with the Declaration of Helsinki. All of the participants provided written informed consent as required by the local Institutional Review Board, according to French regulations for biomedical experiments with healthy volunteers [Ethical Committee of CPP Sud-Est IV (CPP 11/007), ID RCB: 2010-A-01529-30, January 25, 2011].

2.2.2 Odorous stimuli

Eighteen odorants were selected a priori based on their distinctiveness, neutral valence, and relatively low familiarity. The odorants were selected to be distinguishable but hardly identifiable.

They were divided into two sets of 9 odorants each: Set 1 of target odorants and Set 2 of distractor odorants (Table 1). The odorants consisted of essential oils and single - or mixtures of - monomolecular chemicals. Their concentrations were adjusted by two experimenters (authors of the paper: ALS and JP) during successive trials to equalize the subjective intensity of all of the olfactory stimuli. The odorants were diluted using mineral oil (Sigma–Aldrich, Saint-Quentin-Fallavier, France). They were presented in 30-ml brown glass jars (Wheaton France, Aumale, France) in which 5 ml of the odorant solution was placed onto an absorbent made of compressed polypropylene filaments to maximize the exchange area between the odorant solution and the air in the jar.

2.2.3 Spatio-contextual environment

The odorous stimuli were presented within an experimental setup made of four 4-mm-thick gray PVC (polyvinyl chloride) plates (Figure 1A,B). Two plates were positioned as side walls and, in the back, a plate was pierced by a window framing a screen [Fujitsu Siemens A19-2A Scenicview, Moniteur LCD 19.0" (48 cm), 1280 x 1024 pixels]. The floor of the setup consisted of a plate pierced by 36 (6 x 6) regularly distributed circular spots (38 mm in diameter), interspaced every 60 mm. In this experiment, the 18 rear spots were obstructed. The base of each spot was made of a translucent Plexiglas® plate and could be backlit by an amber light-emitting diode located beneath the plate (amber power LED 2.15 V, 20 mA) combined with an additional resistance of 179 Ohms. The setup was controlled using in-house LabView software (version 8.6) with an NI-USB 6509 card (96 5V-TTL channels) with two additional CB-50LP connection blocks and two R1005050-type ASSY cables (National Instruments, Austin, TX, USA).

Nine of the spots were defined as targets, determining the spatial locations of the odors (Figure C). The other nine spots were defined as distractors. When occupied by an odor, the spot was illuminated. Three landscape pictures presented full-screen (1280 x 1024 pixels, 72 dpi) constituted the target contexts (a cliff, a lavender field and a desert, Figure 1D). Every target context had a corresponding look-alike distractor, depicting the same type of landscape but in a different place.

2.2.4 Episodic event

In real-life events, an episode is typically composed of several objects located spatially in a specific environment. To enable the event created within our experimental setup to approach the richness of real-life events as closely as possible, an episode was represented by a subset of three odors (*What*) placed at three specific spots on the board (*Where*) in a specific visual context (*Which context*). To facilitate distinction between episodes, the odor sources (jars) were grouped together in a different part of the plate (left, middle or right). Three episodes were presented in which all three dimensions (*What*, *Where* and *Which context*) differed. Thus, the first subset of odors (odors 1 to 3) was presented in spots in the two left columns and was associated with the cliff picture, whereas the second subset of odors (odors 4 to 6) was presented in spots in the two middle columns and was associated with the lavender field picture. The third subset of odors (odors 7 to 9) was presented in the two right columns and was associated with the desert picture (Figure 1C,D).

2.2.5 Experimental procedure

The experiment was performed in a ventilated and soundproofed experimentation room (3 x 3 m), where the participants were seated in an armchair in front of a table containing the experimental apparatus. The experiment was organized into two phases: an encoding phase during the first three days and a retrieval phase during the fourth day (Figure 2). A full night of sleep was allowed between sessions to promote consolidation (Maquet, 2001; Stickgold, 2005; van der Helm et al., 2011). Each participant completed each session at the same time each day to limit the differential influence of internal state (hunger, satiety) on olfactory and cognitive process between sessions (Jiang et al., 2008; Plailly et al., 2011).

In the encoding phase, episodes were presented for 7 min, one episode per day. The participants were instructed to freely explore the episode by observing the spatial and contextual environment and by smelling the odors as many times as they wished. They were not informed of the objective of the encoding sessions, and therefore were not told to memorize the episode, to ensure a free encoding, closer to what arises in real-life situations. The three episodes were randomly presented

to avoid any confounding factors based on the order of presentation. Each order was used equally between participants.

In the retrieval phase, memory was investigated using two tests. Test 1 included two different tasks: an odor recognition task testing for memory of the odors and an episodic retrieval task testing for memory of the spatio-contextual environment associated with the odors. Test 2 involved a spatio-contextual association recall task, which tested for the strength of the association between the spatial location and the visual context of an event. The retrieval phase was self-paced.

Test 1 consisted of 18 trials lasting at least 30 s, with no maximum time limit, and an inter-trial interval of 5 s. Each trial began with an odor recognition task. One jar containing an odorant was presented, and the participants had to determine verbally whether they had already smelled the odor in the three previous episodes ("Yes" or "No"). The odor could be either target or distractor. Each of the 18 odors was presented once, and the target and distractor odors were presented in a pseudorandom order in such a way that no more than two targets or distractors were consecutively presented. If the participants responded "Yes" (recognition of the odor), their recall of the entire episode associated with this odor was subsequently tested. They were asked to indicate the exact position of the odor by pointing out a location among the 18 spots on the board and a context among the six contexts presented on the screen (Figure 1D). If they responded "No" (rejection of the odor), the experimenter moved on to the next odor. Recollection memory is modulated by the degree of subjective confidence that an event or stimulus has been encountered previously (Koriat and Goldsmith, 1996). For each type of response (odor recognition or rejection, and recall of the spot and context, if applicable), the participants were asked to evaluate subjective confidence using a 0 (chance) to 4 (extremely sure) rating scale.

In Test 2, the participants had to recall the spatio-contextual environment of the three episodes by recalling the association between three spots on the board and one context on the screen. They performed this task for the three target contexts chosen in Test 1 by placing each of three odorless jars on specific spots on the board. A response was considered to be correct when the participants

not only selected a target spot and a target context but also when their association was accurate (i.e., when these spot and context were previously part of the same episode).

2.2.6 Data analysis

Test 1. In the odor recognition task, the numbers of correct and incorrect responses were separately determined for the target and distractor odors. Two-way non-parametric analyses of variance (ANOVAs) (see Wilson, 1956) were conducted to test for the effects of Odor type (target vs. distractor) and Response accuracy (correct vs. incorrect) on the number of responses.

Recognition memory performance was further assessed using parameters from signal detection theory (Lockhart and Murdock, 1970). From the experimental conditions (target vs. distractor) and the participants' behavioral responses ("Yes" vs. "No"), four response categories were defined: Hit and Miss when the target items were accurately recognized or incorrectly rejected, respectively, and correct rejection (CR) and false alarm (FA) when the distractor items were correctly rejected or incorrectly recognized, respectively. In the framework of the signal-detection theory, a memory score (d'_L) reflects the subject's ability to discriminate between target and distractor items, and a response bias score (C_L) reflects the decision rule adopted when responding. These scores determined from Hit and FA scores were calculated as follows:

$$d'_L = \ln (HR(1- FR)/FR(1- HR))$$

$$C_L = 0.5 \text{ x } \ln ((1- FR)(1- HR)/(HR \text{ x } FR))$$

where *HR* represents the Hit rate [(Hit + 0.5) / (N_t + 1)], *FR* represents the false alarm rate [(FA + 0.5) / (N_d + 1)], and N_t and N_d represent the number of target and distractor odors, respectively, for which the participants provided an answer. Memory scores may be good or poor (positive or negative values, respectively). Response bias scores establish three individual attitudes. The participants may be conservative (tending to respond "No"), neutral (responding "Yes" or "No" with equal probability) or liberal (tending to respond "Yes") with positive, neutral or negative values, respectively (Snodgrass and Corwin, 1988).

In the episodic retrieval test, we focused our analyses on the participants' responses for target odors (Hit) but did not take into account responses for the distractor odors that were inaccurately recognized as targets (FA). Four types of responses were defined, depending upon the recall accuracy. When the participants correctly recognized the target odors, they additionally could accurately remember either both the location (the location was considered to be correct when it was included into one of the spots associated with the episode) and the context (WWW), the location only (WWhere), the context only (WWhich), or they could be mistaken about both dimensions (What). These different scenarios were named episodic combinations. The numbers of responses in these episodic combinations were computed, and the data were analyzed using the Friedman non-parametric test (Conover, 1980).

The number of correct responses in the odor recognition (Hit) and in the episodic retrieval (WWW) tasks were separately computed as a function of Day of encoding (day 1, day 2, or day 3) and analyzed using the Friedman non-parametric test (Conover, 1980) to explore primacy and recency effects.

In the odor recognition task, the measures of subjective confidence were averaged as a function of Odor type (target vs. distractor) and Response accuracy (correct vs. incorrect) and were subjected to a two-way parametric Odor type x Response accuracy ANOVA with repeated measurements. In the episodic retrieval task, the measures of subjective confidence given by the participants for the three Dimensions of the episode (odor, location and context) were averaged as a function of Episodic combinations (WWW, WWhere, WWhich, What) and were subjected to a two-way parametric ANOVA with repeated measurements (Winer et al., 1991).

Test 2. In the spatio-contextual association recall task, accurate associations between locations and context (cliff, lavender field or desert) were determined, and the data were subjected to a Friedman non-parametric test to test for the effect of context on response accuracy.

Statistical analyses were performed using Statistica (StatSoft®, Tulsa, OK, USA) and an in-house software program (for two-way non-parametric ANOVA). Effects were considered to be

significant at $p < 0.05$. Statistical tests based on the Chi-squared metric were corrected for ties. When ANOVAs were significant, *post-hoc* comparisons were conducted using bilateral Student *t*-tests for parametric data (Winer et al., 1991) and Mann-Whitney *U*-tests for non-parametric data (Conover, 1971).

2.3 Results

2.3.1 Odor recognition

Figure 3A represents the number of responses calculated as a function of Odor type (target vs. distractor) and Response accuracy [correct (Hit and CR) vs. incorrect (Miss and FA)]. The number of responses varied significantly as a function of Response accuracy [$\chi^2(1,1) = 10.80$, $p < 0.0005$], and the number of correct responses (7.55 ± 1.26, reflecting 84% of responses) were higher than the number of incorrect responses (1.45 ± 1.26). The number of responses did not significantly differ between the target and distractor odors [$\chi^2(1,1) = 0.00$, $p > 0.9$], and no significant interaction was observed between Odor type and Response accuracy [$\chi^2(1,1) = 0.00$, $p > 0.9$]. The number of accurate target odor recognition (Hit) did not significantly change between Day of encoding (2.59 ± 0.09, $\chi^2(2) = 1.82$, $p > 0.4$).

The participants' subjective confidence in their responses is represented in Figure 3B. On average, the participants were confident in their responses (2.89 ± 0.36, on a 0 to 4 rating scale). The subjective confidence varied significantly as a function of Response accuracy ($F(1,11) = 35.32$, $p < 0.0001$), with the participants being more sure of their correct responses (3.19 ± 0.48) than of their incorrect responses (2.59 ± 0.79). No significant effect of Odor type ($F(1,11) = 1.48$, $p > 0.2$) and no Odor type x Response accuracy interaction ($F(1,11) = 0.03$, $p > 0.8$) were found.

The memory score was high ($d'_L = 3.30 \pm 1.37$; the maximal theoretical absolute value equals 5.89), indicating that the participants were proficient at recognizing the target odors and at rejecting the distractor odors. The bias score was close to zero ($C_L = -0.24 \pm 0.59$; the maximal theoretical absolute value equals 2.94), demonstrating that the participants adopted a rather neutral attitude (no tendency to preferentially use either Yes or No responses)

2.3.2 Episodic retrieval

The number of responses differed significantly as a function of Episodic combination (WWW, WWhich, What) [$\chi^2(2) = 44.80$, $p < 0.001$; Figure 4A]. This number was significantly higher for WWW and What than for WWhich ($p < 0.001$ and $p < 0.0001$, respectively) combinations. No response was found for the WWhere combination. The number of accurate episodic performances (WWW) did not significantly change between Day of encoding (1.20 ± 0.07, $\chi^2(2) = 2.16$, $p > 0.3$).

The participants' subjective confidence in their responses differed significantly as a function of Episodic combination [$F(2,14) = 4.06$, $p < 0.05$; Figure 4B], indicating that confidence was significantly higher for WWW than for What ($p < 0.02$). A significant effect of Dimension was also observed [$F(2,14) = 62.70$, $p < 0.0001$; Figure 4C], showing that confidence in responses was higher for both odor and context than for spatial location (*p's* < 0.0001). No significant Episodic combination x Dimension interaction was observed [$F(4,48) = 1.64$, $p > 0.1$].

2.3.3 Spatio-contextual association recall

The participants accurately associated spatial locations and visual context in 2.36 ± 0.93 out of 3 episodes, reflecting 79% correct association. These performance differed significantly depending upon context [$\chi^2(2) = 15.48$, $p < 0.0005$], indicating that the number of accurate associations was higher for the Cliff (2.68 ± 0.65) and Desert (2.45 ± 1.06) contexts than for the Lavender field (1.95 ± 1.09) context ($p < 0.002$ and $p < 0.05$, respectively).

2.4 Conclusion

The results demonstrated that the participants were highly competent at recognizing unfamiliar target odors and were confident in their responses, demonstrating the validity of using odors as recall cues. Moreover, the participants were able to recall the spatio-contextual environment of an episode cued by an odor with a high confidence in their responses. When the episodic responses were inaccurate, most of the errors were due to a failure to recall either both the spatial location and visual context of an odor or to recall the spatial location only, suggesting that the spatial location was the most difficult dimension to recall. Thus, our experimental procedure allows for the study of

episodic memory in a task that combines the free encoding of three unique, complex, tri-dimensional episodes (unfamiliar odor positioned in a specific location within a given context) and their controlled recall 24 to 72 h later.

The goal of Experiment 2 was to adapt this procedure to the context of a future fMRI study exploring neural substrates underpinning episodic memory.

3 **Experiment 2**

3.1 Objective and design

The principal aim of Experiment 2 was to adapt our behavioral approach to episodic memory to the specific constraints associated with fMRI experiments. This adaptation consisted of an increase in the number of trials to improve signal quality. We focused our interest on three conditions: correct rejection of an odor (CR), correct episodic retrieval (WWW) and incorrect episodic retrieval (What). Our secondary goal was to test the influence of odors on memory performance by swapping their functions: target odors were used as distractor odors, and distractor odors were used as target odors. To assess memory performance, the same paradigm was used as in Experiment 1.

3.2 Materials and Methods

3.2.1 Participants

Twenty healthy participants consented to participate in the experiment. These individuals were separated into two groups of ten participants (Group 1, 8 women, 20.6 ± 2.07 years old; Group 2, 5 women, 20.4 ± 1.71 years old), based on which odor sets were presented as targets and distractors in the experiment. No significant differences in age (unpaired Student's *t*-test, $p > 0.8$) or gender (Mann-Whitney *U* test, $p > 0.1$) were found between the groups. The recruitment criteria and ethical considerations were identical to those in Experiment 1.

3.2.2 Stimuli

Both sets of 9 odors were similar to those in Experiment 1, except for Isobutyl quinoline 54. This odor, which was associated with the highest percentage of FAs in Experiment 1 (45% vs. 15% on

the average for the other odors; $\chi^2(8) = 24.66$, $p < 0.002$), was replaced by the Prune aroma (at a concentration of 1%). As a result of this change, in Experiment 2, the FA scores did not significantly differ between odors ($\chi^2(8) = 10.52$, $p > 0.2$). The spatio-contextual environments of the odors were identical to those used in Experiment 1.

3.2.3 Experimental procedure

The encoding phase was the same as in Experiment 1. In the retrieval phase, during the odor recognition and episodic retrieval tasks (Test 1), the odors were repeated several times (5 times for the 9 target odors and 3 times for the 9 distractor odors) to obtain a sufficient number of trials (estimated at 15) for each of the three conditions of interest (WWW, What, and CR). Thus, Test 1 consisted of 72 trials, combining presentations of 45 target and 27 distractor odors. These trials were subdivided into 3 blocks of 24 trials, each with 15 target and 9 distractor odors. In each block, a pseudorandom order was established in such a way that two presentations of the same odor were separated by at least two trials. The block presentation order (6 possible combinations) was counterbalanced between participants. To limit the experiment length, the participants were not asked to rate their subjective confidence in their responses, and a maximum time limit of 30 s per trial was set. Test 1 lasted for 42 min. Test 2 (spatio-contextual association recall) was identical to Experiment 1 and lasted for 5 min.

We tested the effect of odor sets used as target or distractor on memory performance. For Group 1, the Set 1 odorants were defined as the targets (S1t), and the Set 2 odorants were defined as the distractors (S2d). For Group 2, the Set 2 odorants were defined as the targets (S2t), and the Set 1 odorants were defined as the distractors (S1d).

3.2.4 Data analysis

In the odor recognition task (Test 1), correct recognitions (Hits) and correct rejections (CRs) were subjected to Friedman non-parametric tests (Conover, 1971) to test for the influence of the Repetition of target odors (from R1 to R5) and of distractor odors (from R1 to R3) on the number of responses. The data for Misses and FAs were not analyzed because they were complementary to

those of Hits and CRs, respectively. For each category of responses, the differential effect of the odor sets used as target or distractor (S1t/S2d vs. S2t/S1d) was investigated using Mann-Whitney *U*-tests. Finally, we conducted two-way non-parametric ANOVAs (Wilson, 1956) to test for the effects of Odor type (target vs. distractor) and Response accuracy (correct vs. incorrect) on the mean number of responses.

In the episodic retrieval (Test 1), for each episodic combination (WWW, WWhere, WWhich, What), the effects of Repetition and Odor sets on the number of responses were tested with Friedman non-parametric ANOVA. The numbers of responses were then averaged across repetitions and odor sets, and the effect of episodic combination on this variable was analyzed using the Friedman test.

In the spatio-contextual association recall task (Test 2), we analyzed the effect of Context (cliff, lavender field, or desert) on accurate associations with one-way non-parametric repeated-measures ANOVAs and the effect of Odor sets with Mann-Whitney *U*-tests.

3.3 Results

3.3.1 Odor recognition

In the odor recognition task, the numbers of correct recognitions (Hit) and correct rejections (CR) were represented as a function of repetitions of target and distractor odors in Figure 5A. The repeated presentation of odors had no significant effect on the number of correct responses (Hit, $\chi^2(4) = 4.47$, p's > 0.3) but significantly affected the number of correct rejections (CR, $\chi^2(2) = 9.57$, $p < 0.009$). This effect was due to a decrease in correct rejections (and a complementary increase in false alarms) across repetitions (R1/R2, $p < .05$; R1/R3, $p < 0.004$). The odor sets used as target and distractor had no significant effect on the number of correct recognitions (Hit, $p > 0.8$) or correct rejections (CR, $p > 0.4$). The response frequencies were further averaged across repetitions and sets of odors. A significant effect of Response accuracy on the number of responses was observed [$\chi^2(1,1) = 72.20$, $p < 0.0001$], with the participants providing more correct (81.50 ± 12.96%) than incorrect (18.50 ± 12.96%) responses. No significant effect of type of odor [$\chi^2(1,1) = 0.00$, $p > 0.9$]

and no interaction between Response accuracy and Odor type [$\chi^2(1,1) = 0.00$, $p > 0.9$] were observed. No effect of the Day of encoding was observed on the number of accurate target odor recognition (Hit, 84.67 ± 3.59%, $\chi^2(2) = 1.94$, $p > 0.3$). A comparison of the odor recognition performance between Experiments 1 and 2 showed that the numbers of correct recognitions and correct rejections were not significantly different (Mann-Whitney *U*-tests; Hit, $p > 0.4$; CR, $p > 0.6$).

A strong memory score ($d'_L = 2.90 \pm 1.06$; the maximal theoretical absolute value is equal to 8.52) indicated that the participants were highly efficient at recognizing odors that were previously presented during free encoding and at rejecting new ones. The response bias was close to zero ($C_L = -0.15 \pm 0.58$; the maximal theoretical absolute value is equal to 4.26), revealing that the participants adopted a rather neutral attitude. No significant differences were found in memory and response bias scores between Experiments 1 and 2 (Student *t*-tests, $p > 0.2$ and $p > 0.5$, respectively).

3.3.2 Episodic retrieval

The number of responses as a function of episodic combination is represented in Figure 5B. Whatever the type of Episodic combination (WWW, WWhere, WWhich, What), no significant effects of Repetition (from R1 to R5) or of Odor set (S1t/S2d vs. S2t/S1d) were found (Repetitions: $\chi^2(4)$'s ≤ 4.56, p's ≥ 0.3; Odor sets: U's ≤ 48.50, p's ≥ 0.5). For each episodic combination, the numbers of responses were averaged across repetitions and odor sets. A significant effect of Episodic combination was found ($\chi^2(3) = 41.53$, $p < 0.0001$), showing that the number of responses was significantly higher for WWW and What than for WWhich ($p < 0.0009$ and $p < 0.0002$, respectively) and WWhere (p's < 0.0001). No significant effect of the Day of encoding was observed on accurate episodic performances (WWW, 36.00 ± 1.15%, $\chi^2(2) = 0.19$, $p > 0.9$). The numbers of responses for WWW, WWhich and What were not significantly different from those found in Experiment 1 (Mann-Whitney *U*-tests; $p > 0.3$, $p > 0.6$, $p > 0.3$, respectively).

3.3.3 Spatio-contextual association recall

The participants accurately associated spatial locations and visual contexts in 2.35 ± 1.06 out of 3 episodes, reflecting 78% correct association. Associations between spatial locations and visual contexts did not significantly depend on context ($\chi^2(2) = 1.88$, $p > 0.08$) or on Odor sets ($U = 47.50$ $p > 0.8$). These results were not significantly different from those found in Experiment 1 (Mann-Whitney *U*-tests; Cliff, $p > 0.7$; Lavender field, $p > 0.5$; Desert, $p > 0.9$).

3.4 Conclusion

The main goal of Experiment 2 was to increase the number of trials to adapt the experimental procedure for a future fMRI study. The behavioral data showed that the participants had equivalent memory performance and response strategies in Experiments 1 and 2, indicating that multiple presentations of the same odor for recognition and episodic recall did not disturb memory processes. We reached our objective of 15 iterations per condition of interest. Our secondary goal was to swap odorant functions (targets vs. distractors) to test their differential impacts on memory performance. Identical performance in both cases demonstrated that the choice of odorants for target or distractor did not bias the results. In brief, these findings showed that this procedure was successfully adapted to study episodic memory in an fMRI experiment.

4 **Discussion**

The main goal of this study was to create a novel approach to investigate episodic memories. Until now, human episodic memory was either explored separately from real-life situations or was not fully controlled. In the current work, we proposed an intermediate approach to determine the experimental conditions that best evaluate episodic memory and being ecologically valid. This approach allowed the controlled study of trial-unique free encoding, retention delay, and the retrieval of rich and complex episodes composed of unnamable odors (*What*) located spatially (*Where*) within a visual context (*Which context*). The participants were highly competent at recognizing unfamiliar odors encountered during encoding and at rejecting new ones. When a target

odor was recognized, the participants were then able to recall the spatio-contextual environment of the episode in approximately half of the trials, indicating good memory performance regardless of the retention delays of up to 72 h. The repetition of trials, which is required for the use of this paradigm in an fMRI study, did not interfere with the recognition or episodic recall processes.

4.1 Odor recognition

Because episodic recall was cued by an odor, the participants had to accurately perform an odor recognition task before subsequently recalling the spatio-contextual environment associated with the odor. Indeed, the participants were proficient at recognizing target odors that had been freely encoded, after retention delays ranging from 24 h to 72 h, while accurately rejecting distractors. Accuracy, memory scores and correct response confidence were all high, and the participants were not biased toward a conservative or a liberal attitude. These data indicate that our odors were good retrieval cues. The current recognition scores were consistent with those observed in earlier studies, demonstrating that 75% to 85% of odor recognition were correct after one week of retention delay (Engen and Ross, 1973; Lawless and Cain, 1975; Lawless, 1978) and that memory scores (d'_L) were similar (Rabin and Cain, 1984). Nevertheless, odor recognition performance strongly depends on experimental conditions, and our scores must be evaluated in light of the specificities of our protocol, as described below.

On the one hand, several aspects of our experimental design facilitated our task. First, it has been reported that odor set size and odor similarities both affect odor recognition: a greater number and similarity among odors results in lower scores (Jehl et al., 1994; Schab, 1991). In our approach, odor recognition was promoted by a quite small sample of odors (9 target and 9 distractors), each of which was easily distinguishable. Second, our encoding sessions lasted for 7 min, and we allowed the participants to smell the odors as often as they wished, in contrast to most odor recognition protocols which present the odors only once and never for longer than 30 s. Third, our maximal retention delay was 72 h, which may be considered to be short in comparison with retention delays of up to 1 month in previous studies.

On the other hand, our task was rendered more difficult by several aspects of our experimental design. The first and most important limiting factor was our choice of odors. Indeed, we intentionally selected unfamiliar and largely unidentifiable odors, which is part of olfactory memory specificity in everyday conditions. Although performance in odor recognition is strongly and positively dependent on familiarity, and therefore is dependent on odor-naming ability and consistency (Bhalla et al., 2000; Frank et al., 2011; Jehl et al., 1995, 1997; Larsson, 1997; Lesschaeve and Issanchou, 1996), our choice was guided by a desire to favor the use of perceptual cues and to minimize associations with verbal labels when exploring the olfactory dimension of the episodes. Moreover, we used neutral odors, with no emotional content, whereas evidence suggests that the valence, and more specifically, the unpleasantness of odors, improves the robustness of memories (Larsson et al., 2009). The second aspect concerned our encoding procedure. We used a free encoding, giving the participants no explicit instructions about memory tasks and simply asking them to freely explore the episodes for 7 min. Both simple odors and memories are typically non-intentionally acquired in ordinary life; however, they are incidentally encoded through unique or repeated exposure. When participants are unaware of an impending memory test, they do not develop learning strategies (Schab, 1991), which is in agreement with the definition of episodic memory formation but which also makes the tasks more complex. Finally, odors were presented several times during the retrieval phase, which increased familiarity (Jehl et al., 1995; Delplanque et al., Personal communication). The data from Experiment 2 showed that the repeated presentation of the distractor odors resulted in an increase in false alarms. Repeated presentation apparently increased the distractors' familiarity and thus increased their likelihood of being misidentified as target odors. Nevertheless, multiple presentations of target odors did not impact their recognition, suggesting that the recognition of target odors was not based on a feeling of familiarity.

In conclusion, despite using odors that were unfamiliar, largely unidentifiable and freely encoded, the participants achieved high recognition scores. These data make odors suitable cues for memory recall in our experimental conditions. Because the participants' globally high abilities at

recognizing odors could not account for all of the above-mentioned features of our protocol, we hypothesize that these good performance reflected the episodic nature of our task. When exploring the episodes, the participants were experiencing a new, rich and complex event, greatly resembling the process by which they form a new episodic memory in a real situation, which enhanced the strength of the odor memory trace.

4.2 Episodic retrieval

In contrast to odor recognition memory, odor associative memory has received scant attention in the literature. When studied, this topic only concerns the association of an odor and a single other item. Odor source memory has been investigated by asking participants to explicitly remember either a specific room (Takahashi, 2003) or a specific space on a board (Gilbert et al., 2008; Goodrich-Hunsaker et al., 2009) in which the odors were presented or to remember the gender of the experimenter presenting the odors (Gilbert et al., 2006; Hernandez et al., 2008; Pirogovsky et al., 2007) during the encoding phase. With a limited number of items (from 6 to 16) and a brief retention time (equivalent to the inter-stimuli interval), performance on average varied from chance performance to 83% correct responses, depending upon the experiment. These findings demonstrate the capacity of healthy volunteers to retrieve associations between two items, including an odor. However, the gap between odor source memory and odor episodic memory is wide and the necessity to elaborate new paradigms to investigate episodic memory is crucial.

Our paradigm is the first to explore odor episodic memory. Our behavioral data demonstrate that the participants were able to recall the spatio-contextual environment (composed of both a picture and a spatial location) of episodes cued by odors in approximately half of trials, which is well above the chance level, and with a relatively high confidence level in comparison with inaccurate recognition. This observation suggests that when an association between odors, spatial locations and contexts is encoded, the association forms a meaningful entity for the participants. Incorrect responses were mainly due to the participants' inability to remember both the spatial and contextual environment associated with target odors. Indeed, the spatial and contextual dimensions of

environments were highly associated (79% and 78% correct associations in Experiments 1 and 2, respectively), demonstrating that either the participants remembered the entire environment or that they were unable to recall any dimensions associated with the odor.

Current data give an experimental proof of the Proust Phenomenon and are in agreement with autobiographical memory studies showing that odors evoke rich and complex memories (Chu and Downes, 2000, 2002; Herz, 2004). Similarly, in a controlled setting, Aggleton and Waskett (1999) reported that visitors to a museum remembered more details of their visit in the same olfactory context as the one in which they incidentally experienced in the museum many years beforehand. These results demonstrated the effectiveness of odors at reviving late memories that were unintentionally learned. More recently, Yeshurun et al. (2009) showed the privileged brain representation of first olfactory associations. In our paradigm, because the odors were especially unfamiliar, we could assume that most of the participants associated these odors with a spatio-contextual environment for the first time. Therefore, the current high number of episodes recalled in their entirety could also result from the low familiarity of our odors.

Our protocol, which is halfway between conventional laboratory and autobiographical approaches, fills a gap for researchers in the memory domain (McDermott et al., 2009). Other novel approaches to episodic memory have also been developed recently. Milton et al. (2011) used SenseCam, an automatic wearable camera that allows the investigation of recognition memory for daily life events. In this approach, the episodes were complex and autobiographical, but the encoding was explicit, and the memories were not freely recalled. Pause et al. (2010) suggested a protocol founded on the *What, Where, When* concept (Tulving, 1972). Their three episodes consisted of objects (visual stimuli) presented at specific locations (quadrants on a screen) at a specific time (day of sessions). The encoding of episodes was strengthened by a specific context story provided prior to stimuli presentation. The episodes were, however, accordingly sharply semantic and had lost many of their episodic features. Holland et al. (2011) also submitted a *What, Where, When* memory task, in which the participants had to remember the locations in which they

chose to hide coins on two consecutive days. The two episodes were very similar, with the participants hiding the same coins in the same room, but in different places. Therefore, the *What* and *Where* dimensions of the episodes were subject to reactivation and reconsolidation, which cast their episodic nature into doubt. Our protocol was designed to avoid these drawbacks as much as possible. We deliberately chose to arbitrarily link odors, spatial locations and visual contexts in each episode to limit associative semantic processes during encoding and recall, even though this choice increased the difficulty of the task.

Our protocol is heavily inspired by episodic-like memory tasks used with animals and focused on a content-based description of episodic memory (Clayton et al., 2001; Easton and Eacott, 2008). These approaches do not investigate subjective experiences associated with episodic recall (Tulving, 1983), which are often accepted as peculiar to humans. In humans, conscious recollection implicated in episodic memory is typically studied with the *Remember/Know* paradigm (Yonelinas, 2001). Either participants *remember* the stimulus in its context, the encoding event (i.e., recollection), or they just *know* they have encountered it before (i.e., familiarity). In our protocol, we did not ask the participants about their subjective experiences when they recognized odors and when they recalled their associated environments. Therefore, we could not maintain that conscious recollection occurred. Considering odor recognition, the multiple presentations of the distractor odors enhanced their level of familiarity, and consequently induced a higher rate of inaccurate recognition of target odors, which suggests that odor recognition was partly based on a feeling of familiarity. Larsson and colleagues (2006) reported that both familiarity and recollection take part in odor recognition. Considering episodic memory of olfactory events, no assumption can be made from our data. Nevertheless, Easton et al. (2012) recently revealed that in *What/Where/Which*, but not in *What/Where/When* episodic tasks, participants had to use recollection to retrieve memory. This finding lends credence to the episodic nature of our protocol, although we still need to test our assertion directly in a future study.

Additionally to the three-dimensional content of the episodic memories, Clayton et al. (2003) argued that these memories must be also integrated, flexible and trial unique. In our case, the episodic memories were unique and contained multidimensional information which the participants form an integrated representation. Indeed, the presentation of the old odors engendered the retrieval of both their contexts and locations in more than 30% of trials, reflecting that an integrated 'what-where-which context' representation had been established. However, flexibility of the episodes is impossible to test with the current protocol and we cannot judge for episodic memory ability to interact with general knowledge.

4.3 Conclusions

To conclude, our current studies first validated our protocol for investigating the memory of olfactory episodes in a fully controlled manner that was as close as possible to real-life situations and demonstrated its reproducibility. Second, we demonstrated our protocol's adaptability to the constraints of an fMRI approach, which will allow us in the future to explore the neural networks implicated in odor recognition memory, which have been seldom investigated (Cerf-Ducastel and Murphy, 2006; Royet et al., 2011; Lehn et al., in press), and the as-yet-unexplored neural bases of odor episodic memory.

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7 Tables

Table 1 List of odorants for sets 1 and 2.

Set 1: Target odorants			Set 2: Distractor odorants		
Number	Label from company	Conc. (%)	Number	Label from company	Conc. (%)
1	Sandalore	4.0	1	Citronellol	1.0
2	Rose oxide	2.0	2	Isobutyl quinoline 54	1.0
3	Stemone	3.0	3	Linalyl acetate	1.0
4	Styrallyl acetate	2.0	4	Nonanal	1.0
5	Carrot	2.0	5	Turpentine	3.0
6	Butanol	0.5	6	Ethyl acetoacetate	1.0
7	Dihydromyrcenol	1.0	7	Basilic (Comoros, EO)	2.0
8	cis-3-Hexenyl salicylate	3.0	8	Allyl amyl glycolate	1.0
9	Methyl octine carbonate	1.0	9	Rosemarel	3.0

Conc., concentration in volume (%); EO, essential oil.

8 Figures

Figure 1

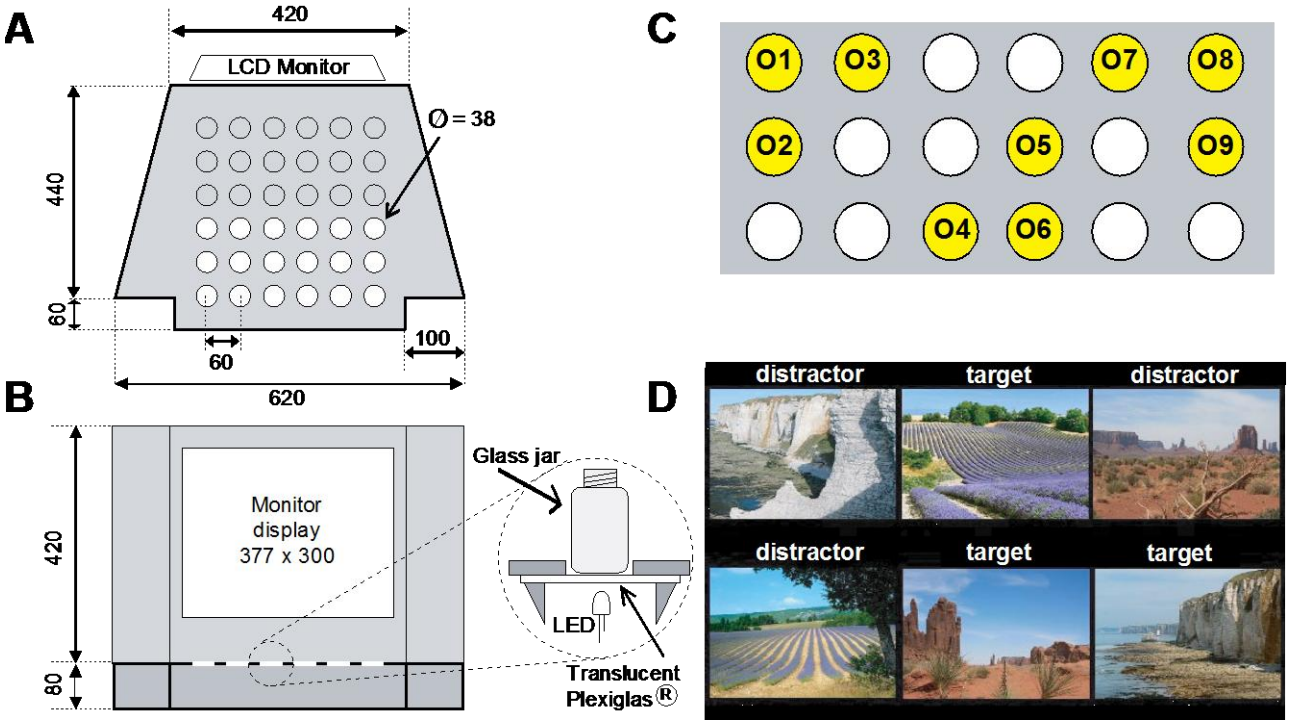


Figure 2

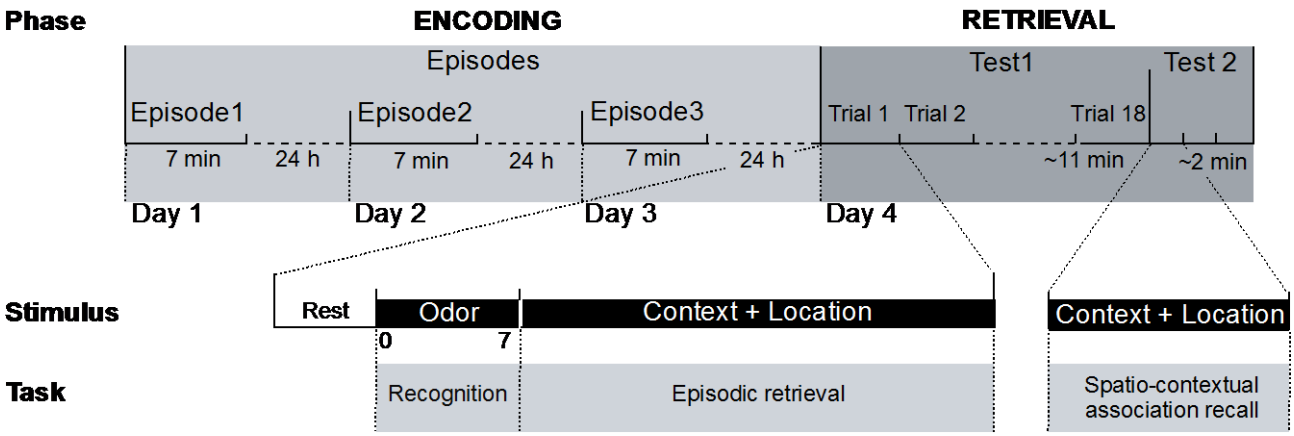

Phase
ENCODING
RETRIEVAL
Episodes
Test1
Test 2
Episode1
Episode2
Episode3
Trial 1
Trial 2
Trial 18
7 min
24 h
7 min
24 h
7 min
24 h
~11 min
~2 min
Day 1
Day 2
Day 3
Day 4
Stimulus
Rest
Odor
Context + Location
0
7
Context + Location
Task
Recognition
Episodic retrieval
Spatio-contextual association recall

Figure 3

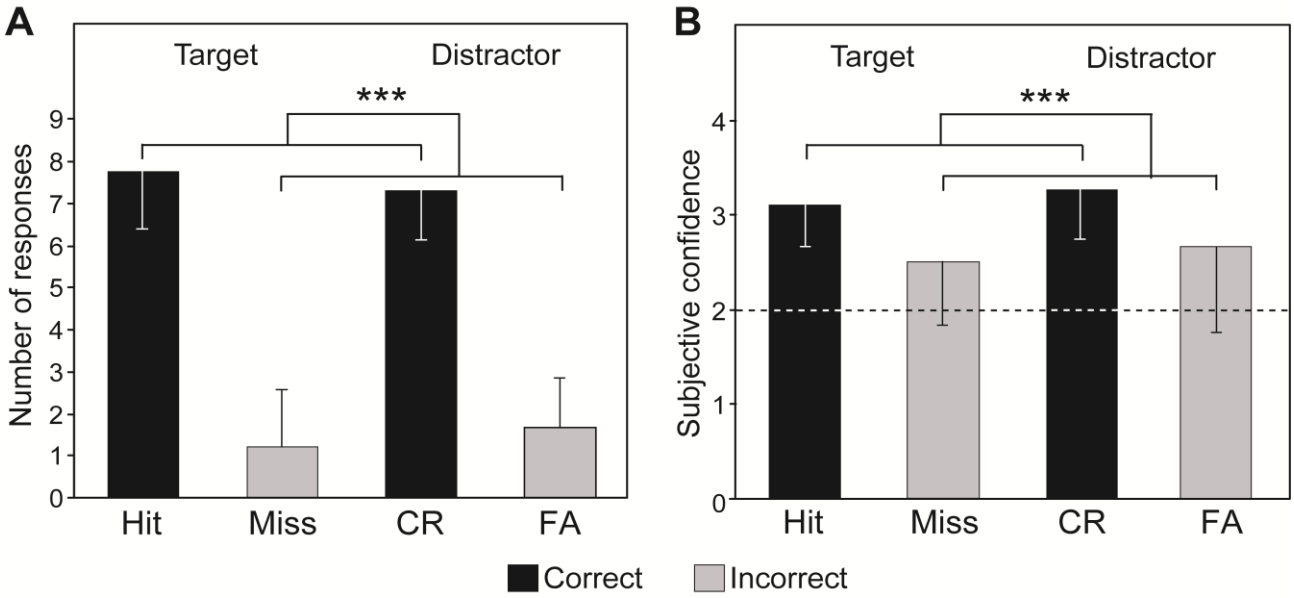
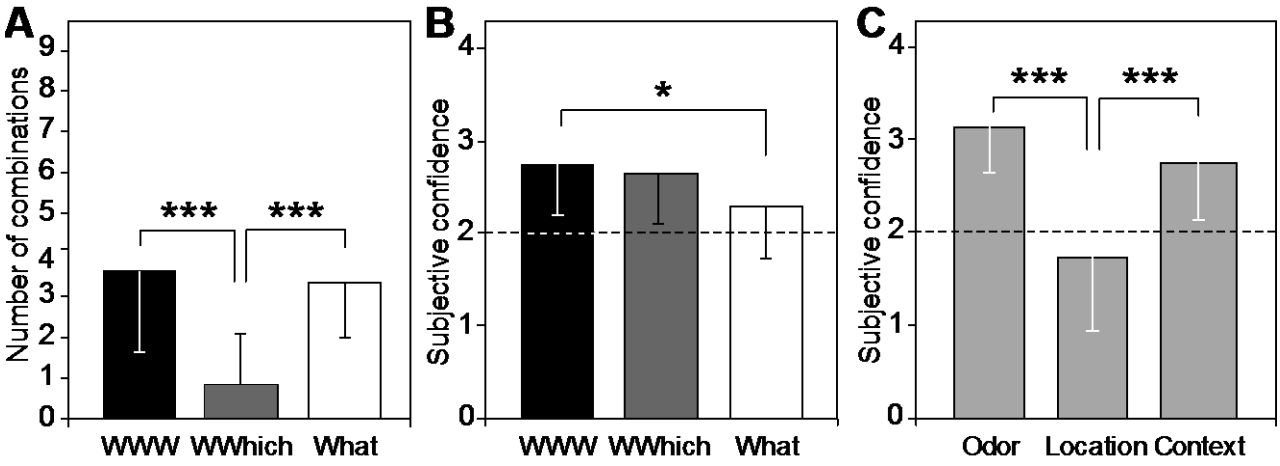

A
Target
Distractor
***
Number of responses
0
1
2
3
4
5
6
7
8
9
Hit
Miss
CR
FA
B
Target
Distractor
***
Subjective confidence
0
1
2
3
4
Hit
Miss
CR
FA
Correct
Incorrect

Figure 4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Number of combinations
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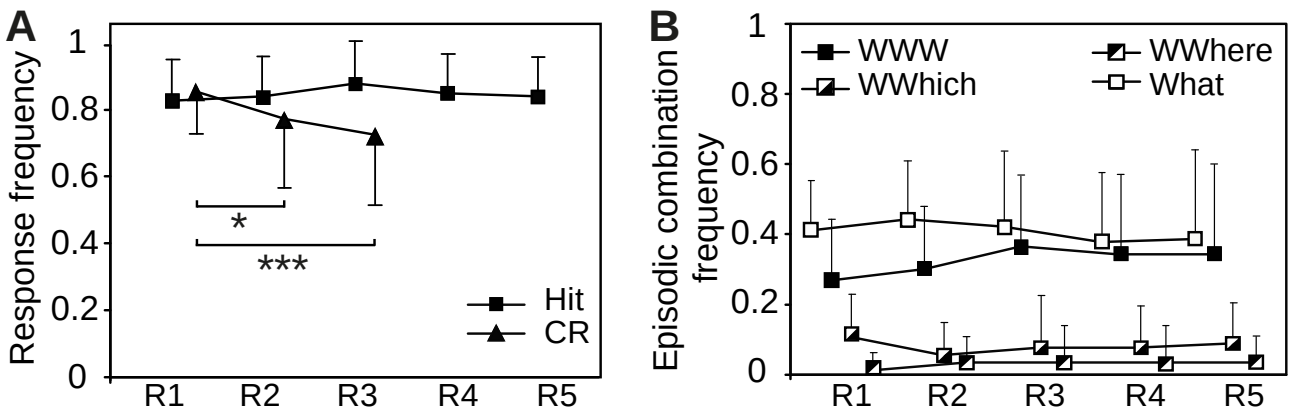
1
2
3
4
5
6
7
8
9
***
***
WWW
WWhich
What
B
Subjective confidence
0
1
2
3
4
*
WWW
WWhich
What
C
Subjective confidence
0
1
2
3
4
***
***
Odor
Location
Context

Figure 5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0.6
0.4
0.2
0
R1
R2
R3
R4
R5
*
***
Hit
CR
B
Episodic combination frequency
1
0.8
0.6
0.4
0.2
0
R1
R2
R3
R4
R5
WWW
WWhere
WWhich
What

9 Legends

Figure 1. A schematic representation of the experimental setup (dimensions are in mm). (A) A view from the top and (B) a view from the front with a zoom on a spot with a LED and a jar. (C) The spatial location of the nine target odors (from O1 to O9) on the board for each episode (O1-O3, cliff context; O4-O6, lavender field context; O7-O9, desert context). White spots represent distractor spots. (D) The three target and the three distractor visual contexts.

Figure 2. Experimental design. The temporal course of the encoding (3 episodes) and retrieval phases (Tests 1 & 2). In Test 1, each trial includes a recognition task, and if the participants respond 'Yes', an episodic retrieval task, Test 2, consists of a spatio-contextual association recall task.

Figure 3. Behavioral results for odor recognition. (A) The mean number of correct (Hit, CR) and incorrect (Miss, FA) responses for the 9 target and 9 distractor odors. (B) The mean subjective confidence in correct and incorrect responses for the target and distractor odors. The dashed horizontal line indicates the mean value of confidence. The error bars represent standard deviations. ***, $p < 0.001$.

Figure 4. The behavioral results for episodic retrieval. (A) The mean number of episodic combinations for the 9 target odors. (B) The mean subjective confidence as a function of episodic combinations. (C) The mean subjective confidence as a function of dimensions. The dashed horizontal line indicates the mean value of confidence. The error bars represent standard deviations. *, $p < 0.05$; ***, $p < 0.001$.

Figure 5. The behavioral results for odor recognition and episodic retrieval across repetitions. (A) The mean frequencies of correct responses for target (Hit) and distractor (CR) odors during repetitions (R1 to R5). (B) The mean frequencies of the four types of episodic combinations during repetitions (from R1 to R5). The error bars represent standard deviations. *, $p < 0.05$; ***, $p < 0.001$.