A new test of value-modulated attentional bias in mice

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Abstract

The allocation of attention can be modulated by the emotional value of the stimulus. In order to understand the biasing influence of emotion on attention allocation further, we require an animal test of value-modulated attention capture evoked by ethologically valid stimuli. In mice, female odour triggers arousal and elicits emotional responses in males. Here, we determined the extent to which objects infused with female odour captured the attention of male mice. Seven experiments were conducted, using a modified version of the spontaneous Novel Object Recognition task. Attention was operationalised using differential exploration time of identical objects that were infused with female mouse dour (O+), infused with almond odour (Oa), or not infused with any odour (O-); and non-infused novel objects (X-). We found that when single objects were presented, as well as when two objects were presented simultaneously and thus competed with each other for attention, O+ captured attention preferentially compared to O-. This was the case both when O+ were placed in a novel location and when they were placed in a familiar location. When compared with Oa at novel location, O+ at familiar location attracted more attention. Compared to X-, O+ captured more attention only when they were placed in a novel location, but attention to O+ and X- was equivalent when they were placed in a familiar location. These results demonstrate that in mice, female odour can in some circumstances capture more attention than non-ethologically relevant olfactory stimuli and object novelty. The findings of this study pave the way to using motivationally-significant odours to modulate the cognitive processes that give rise to novel object recognition.

Keywords: attention, emotional arousal, memory, Novel Object Recognition task, olfactory stimuli

Introduction

Emotional arousal influences cogitation extensively, from early perception, to attention (Golomb, Nguyen-Phuc, Mazer, McCarthy, & Chun, 2010; Pourtois, Schettino, & Vuilleumier, 2013), to higher order cognitive functions (Pessoa, 2009), including memory (Levine & Edelstein, 2009; Talmi, 2013). A central objective of human neuropsychological and neuroimaging research is to trace the neurobiological underpinnings of the link between emotional arousal and attention (Hartikainen, Ogawa, Soltani, & Knight, 2007; Kadohisa, 2013; Lee, Sakaki, Cheng, Velasco, & Mather, 2014; Talmi & McGarry, 2012; Vermeulen, Godefroid, & Mermillod, 2009). In line with this objective, the present study was designed to investigate the impact of an emotionally charged stimulus on attention allocation in mice. Establishing the means to measure such a link would provide a valuable animal task with which to further understand the neurobiology of emotional memory and attention.

Attention is crucial for the effective processing of perceptual information presented by the environment at any given time (Chun, Golomb, & Turk-Browne, 2011). Behaviourally-relevant stimuli are thought to be selected against others and prioritised via two routes: top-down and bottom-up (Corbetta, Patel, & Shulman, 2008; Miller & Cohen, 2001; Pratt & Hommel, 2003). Endogenous attentional control, also referred to as *goal-directed* or *top-down*, is a voluntary process that operates at the level of memory and decision making to modulate information according to the agent's intentions. In contrast, the exogenous, involuntary attentional capture by certain stimuli, known as *bottom-up* or *stimulus-driven attentional process*, depends on the physical characteristics of stimuli and is outside the agent's control. A recently proposed model, called Multiple Attention Gain Control (MAGiC), suggests a third route to attentional selection, through emotion. Emotion is thought to bias perception via distinct gain control mechanisms originating in the amygdala. Neuropsychological, neuroimaging and behavioural studies have provided evidence for the modulatory effects of emotion on sensory processing, whereby emotionally charged stimuli acquire increased representation and access to awareness compared to neutral stimuli (for review, see Pourtois et al., 2013). The majority of studies that informed the MAGiC model utilised threat-related stimuli, due to their obvious behavioural salience (Compton, 2003; Vuilleumier, 2005), as well as their role in various pathological conditions in humans, such as anxiety and phobias (Öhman & Mineka, 2001). However, in order to achieve a more complex understanding of the influence of emotion on the selection of sensory information, more research is needed on the effects of other emotional stimuli on attention, including those with positive value.

Stimuli that predict a valuable outcome – whether positive or negative - capture attention automatically, even when they are task-irrelevant (Anderson, Laurent, & Yantis, 2011; Wang, Duan, Theeuwes, & Zhou, 2014; Wentura, Müller, & Rothermund, 2014). This value-derived influence on

attention is neither top-down, nor bottom-up, since attention in this case is neither voluntarily directed by contextually relevant goals, nor driven by the sensory significance of the stimuli, respectively. Rather, attention is directed to stimuli that have acquired the potential to predict valuable outcomes via associative learning. This mechanism is referred to as *value-modulated attentional capture (VMAC)* (Le Pelley, Mitchell, Beesley, George, & Wills, 2016). While prioritising unexpected high-value stimuli might be biologically advantageous in certain situations, in others it could interfere with goal-directed behaviours. Further research is needed to offer a more in-depth understanding of the computational control of VMAC (Talmi, Slapkova, & Wieser, 2018).

The neural basis of top-down and bottom-up attention has been studied in detail in humans and in animal models. In humans, the majority of studies have been conducted on visual attention. Endogenous (top-down) signals arising in higher-order prefrontal, parietal and limbic cortices interact with exogenous (bottom-up) signals driven by visual cortical pathways to bias attention in favour of attended targets, while suppressing representations of unattended information (Desimone & Duncan, 1995; Gitelman, 2003; Katsuki & Constantinidis, 2014). Across the literature, goal-directed attentional processing has been generally attributed to dorsal fronto-parietal brain areas, while stimulus-driven attentional control is believed to be mediated by ventral temporal-parietal networks (Anderson, Laurent, & Yantis, 2014; Corbetta & Shulman, 2002; Yantis et al., 2002). Animal studies of sustained attention, particularly in task-performing rats, have revealed the role of the cholinergic system in top-down, as well as bottom-up attentional control. The basal forebrain corticopetal cholinergic projections, which are activated via direct glutamatergic inputs from the prefrontal cortex to the basal forebrain, terminate in all cortical areas and are thought to mediate top-down processes in tasks involving sustained attention (McGaughy & Sarter, 1998; Sarter, Givens, & Bruno, 2001; Zaborszky, Gaykema, Swanson, & Cullinan, 1997). Lesions of the basal forebrain, affecting inputs of acetylcholine particularly in fronto-dorsal cortical areas of rat models of attention, result in prolonged impairments of sustained attention (Sarter et al., 2001). Bottom-up attentional processes have been shown to largely depend on noradrenergic projections, which originate in the locus coeruleus and terminate in the thalamus and the basal forebrain. Noradrenergic activation of basal forebrain corticopetal projections is involved in the processing of threat-related or anxiety-inducing stimuli in a bottom-up fashion via the recruitment of telencephalic systems (Aston-Jones, Rajkowski, Kubiak, Valentino, & Shipley, 1996; Sarter et al., 2001). So far, these animal studies have demonstrated that the basal forebrain cortical cholinergic system represents a core component of the neuronal circuitry involved in attentional processing, thus contributing to the understanding of the role of the fronto-parietal cortical regions from human neuropsychological and imaging research. Integrating evidence from human and animal works is necessary for the development of a reliable model of the neural mechanisms of attention.

The neural basis of VMAC has been less well understood in animal models. In humans, Anderson et al. (2014) argue that the neural mechanisms underlying VMAC are mediated by the tail of the caudate nucleus and the extrastriate visual cortex. Using functional magnetic resonance imaging (fMRI), these researchers found that task-irrelevant reward-predictive stimuli acting as distractors acquired stronger representation in the caudate tail and triggered greater activity in the extrastriate visual cortex versus other non-target stimuli. So far, animal models of attention using stimuli with emotional value have been derived from the traditional theories of associative learning and conditioning. In one model of associative learning, proposed by Mackintosh (1975), animals pay more attention to cues that are reliable predictors of a consequence (high predictiveness) than to non-predictive cues. Selective attentional bias towards good predictors allows animals to focus on relevant cues, while ignoring distractors, thereby achieving optimal performance. In contrast, the model by Pearce and Hall (1980) states that cues with uncertain consequences capture the most attention. The idea behind this model is that because unreliable cues are surprising, they will be allocated more attentional resources that leads to rapid learning about their significance. While there is abundant evidence in favour of both predictability (Duffaud, Killcross, & George, 2007; George & Pearce, 1999) and uncertainty (Kaye & Pearce, 1984; Wilson, Boumphrey, & Pearce, 1992) models, several hybrid models have emerged in an attempt to reconcile these principles (for reviews, see Esber & Haselgrove, 2011; Le Pelley et al., 2016). To date, very little, if any, data exist on the influence of biologically relevant stimuli on VMAC in rodents. The present study is, to our knowledge, the first research using female odours to examine VMAC in a rodent model of attention.

Unlike humans, who are predominantly influenced by visual stimuli (Shapiro, Egerman, & Klein, 1984), most mammals, including rodents, rely mainly on odours to obtain information about their environment (Brennan & Kendrick, 2006; Johnston, 2003). Odours from conspecifics of opposite sex are thought to carry positive reward values, because they elicit an approach response to promote reproductive behaviours, as opposed to withdrawal or avoidance responses, which supress reproductive behaviours (Beny & Kimchi, 2014). The motivational significance of odours bearing reproductive value does not seem to depend on the animal's prior sexual experience; these stimuli can, therefore, be considered primary reinforcers. This is evident in the laboratory, where sexually inexperienced male rodents display typical sexual behaviours when exposed to female odours (Beny & Kimchi, 2014). Given the socio-biological relevance of odours and their known motivational effects on animals, it is reasonable to assume that odours could be used as stimuli to investigate VMAC in an animal model.

Seven experiments were designed to quantify the degree of attention allocation in male mice to objects infused with female odour (O+). We contrasted the O+ objects with odour-neutral objects (O-), novel objects (X-) and objects infused with almond extract (O^a), a mildly attractive odour for

rodents (Huckins, Logan, & Sanchez-Andrade, 2013). These objects were used in a modified version of the spontaneous Novel Object Recognition (NOR) task. NOR is one of the most widely used paradigms in studies of memory functions in rodents. The NOR task can be configured to measure attention (Silvers, Harrod, Mactutus, & Booze, 2007) and has been used in studies focusing on pathological conditions or drug abuse, which result in attentional deficits (Alkam et al., 2011; Piper, Fraiman, & Meyer, 2005). Originally developed by Berlyne (1950) and subsequently adapted for use in mice by Murai *et al.* (2007), this behavioural task relies on the drive of rodents to explore novelty in the absence of any training or external reinforcers. The original NOR task comprises three phases: habituation, familiarisation and test. In the first two phases, the animal is exposed to an open-field arena (habituation) and then to the same arena in the presence of two identical objects (familiarisation). The test phase is similar to the familiarisation phase, with the exception that one of the identical objects is replaced with a novel object. Healthy adult rodents recognise the familiar object at test and pay more attention to the novel (more arousing) object, indicated by a longer exploration time of the novel versus familiar object (Ennaceur, 2010; Gaskin et al., 2010; Mumby, Glenn, Nesbitt, & Kyriazis, 2002). In the modified NOR paradigm used in this study, instead of novel and familiar objects, the attention allocation of male mice was investigated for O+ versus O-, O^a or X-, which were placed in either novel or familiar locations in a Y-maze.

The first two experiments assessed the attentional capture of mice by an O+ compared with an O, when both objects were novel (Experiment 1) or familiar (Experiment 2). We hypothesised that because the motivational value of O+ was higher than of O-, the former would attract more attention in both experiments. We then asked whether the same would be true if O+ and O- were placed at different locations in the arena, so that O+ would be found at either a novel (Experiment 3) or a familiar (Experiment 4) location. In these experiments, novel location was used due to its previously demonstrated influence on attention (Ennaceur, Neave, & Aggleton, 1997) and, thus, it was interesting to study how well novel location competed with female odour for attention allocation. We hypothesised that when the location of O+ was novel, O+ would capture more attention than O-, because the former benefited from the advantage of two salient motivational features, namely, motivational value and novel location. However, in Experiment 4 it was less clear whether O+ would still 'win' over O-, due to the fact that the novel location of the latter was now competing with the odour of the former for attention. In the next two experiments, we used another well-known motivational feature, novel object identity, and assessed how strong the attention capture by odour was when competing with a novel object (X-). Novel objects are expected to recruit more attention than familiar objects in the traditional NOR task and, therefore, we were interested to test how attention to O+ would be influenced by the presence of X-. Experiment 5 tested the attention captured by O+ at a novel location versus an X- at a familiar location. Here, O+ had the advantage of odour and location novelty, while X- had the advantage of novel identity. In Experiment 6, X- was placed at

a novel location and O+ at a familiar location. Since this time X- had the advantage of both novel identity and novel location, the question was whether it would attract more attention than O+.

There is preliminary evidence that social odour captures more attention in mice compared to non-social odours. Rattazzi, Cariboni, Poojara, Shoenfeld, & D'Acquisto (2015) compared female mouse odour and other social odours to non-social odours in male mice of a similar strain to the ones used here, and which were obtained from the same provider. They found that control mice, as well as immune-cell deficient recombination-activating gene (RAG-1) knockout mice, showed increased sniffing time for the former. Therefore, in Experiment 7, we wanted to compare the degree to which objects infused with female odour attracted more attention than objects infused with another odour with a lower level of motivational significance.

In their study on the effects of odour preferences on rats' discrimination learning, Devore, Lee, & Linster (2013) classified 53 monomolecular odorants as *high*, *neutral* and *low*, in terms of spontaneous odour preferences. By contrast, the odour of flowers, nuts and fruit is a mixture of compounds. For the purposes of our study, instead of single chemical compounds, we decided to use the odour from a compound mixture (such as a flower, nut or fruit), because such odours are prevalent in behavioural studies of mice (Arbuckle, Smith, Gomez, & Lugo, 2015; Rattazzi, Cariboni, Poojara, Shenfeld, & D'Acquisto, 2015; Yang & Crawley, 2010). We selected almond odour, one of those used by Rattazzi et al. (2015). According to (Huckins, Logan, & Sanchez-Andrade, 2013), unlike conspecific urine smell, which is a 'social odour' and, therefore, high in motivational significance, the odour of almond extract is mildly motivationally significant, since it is a natural food odour but distinct from the food laboratory mice are used to. This type of odour can be employed as a neutral non-social odour alongside social odours in rodent experiments investigating odour-mediated behaviour and odour identification ability (for instance, when testing deficits in identifying pleasant or neutral odours in rodent models of psychiatric diseases, Huckins, Logan, & Sanchez-Andrade, 2013). We predicted that despite the mild motivational significance of almond odour, animals in Experiment 7 will allocate more attention to female mouse odour.

In Experiment 7b attention allocation to O+ at a familiar location was compared to attention allocation to O^a at a novel location. Here, O+ had the advantage of motivational significance, while O^a benefited from two factors, namely location novelty and a mildly attractive odour. This experiment compared the attentional draw of two different odours, in contrast with the previous two experiments, which compared an olfactory stimulus with visual stimuli. Similar to Experiments 5 and 6, in this last experiment it was interesting to observe which object feature combinations captured more attention and whether O+ can still elicit more interest.

Unlike previous research which used social and non-social odours to look at the animal's capacity to distinguish between the two and to investigate habituation/dishabituation (Arbuckle, Smith, Gomez, & Lugo, 2015; Yang & Crawley, 2010), or to test altered sense of smell in certain conditions (Rattazzi, Cariboni, Poojara, Shenfeld, & D'Acquisto, 2015), our study focused on quantifying the attentional capture by a social odour and provided a reliable protocol for future studies using NOR in such behavioural assessments.

Methods

Animals

Behavioural experiments were performed using eight adult male C57BL/6J mice (Charles River, UK), which were 14 weeks (3.5 months) old at the start of the experiments and weighed 30±3 g throughout the project. Mice were weighed prior to each experiment and at the end of the last experiment on a laboratory scale (Kern FCB, Germany). Mice were maintained by the Biological Services Facility (BSF), University of Manchester, UK and housed in groups of four individuals in ventilated Techniplast cages, in standard conditions (20°± 2°C temperature and 55±5% humidity) on a 12:12 light/dark cycle, with *ad libitum* access to food and water. All mice were ear punched for identification. The experiments were carried out over a period of two months and took place between 9:30am-12:30pm. All procedures were conducted in conformity with the University of Manchester BSF regulations for animal husbandry and with the Home Office Animals (Scientific Procedures) Act (1986) and were licenced by the UK Home Office and University of Manchester Ethical Review Panel.

Apparatus

Experiments were performed in custom Y-mazes with three identical white, opaque plastic arms, (length 160mm, height 280mm) diverging at a 120° angle from each other (designed by Jack Rivers-Auty and constructed by Plastic Formers Ltd, UK). Each arm became wider at the end to form a small square arena (length 92mm x width 90mm). The square arenas could be differentiated by the presence of salient visual cues. Individual mice were randomly assigned to a particular Y-maze throughout habituation and testing. Mice were always released inside the middle arm (the arm closest to the nearest room wall), with their backs to the right and left arms, which contained objects (see Materials). This strategy, following the guidelines by Antunes and Biala (2012), ensured that external pressure to explore the objects was avoided. During the interval between exposures (habituation) and the inter-trial interval (ITI, experiments), mice from each cage group were placed in separate holding cages (standard housing cages, Techniplast), which remained the same throughout the project. Mice

from each cage group were run simultaneously in four Y-mazes placed next to each other. Video cameras (JVC, 40x optical zoom) placed above the Y-mazes recorded animal performance.

Materials

The objects used in experiments were either built from LEGO® pieces or various other plastic shapes (Figure 1). Given that the egg halves were identical in shape, the difference in their colour as well as their position in the maze (face-down or on one side with either convex or concave side facing the animal) were used to create different object types. All objects were odour-neutral and made of plastic in order to avoid material preference, minimise odour saturation and facilitate cleaning. The objects were attached to the floor inside the Y-maze with Blu-Tack®. Objects used in the habituation phase were plastic letters and were never used in subsequent experimental trials. New object types were used in each experiment, in order to avoid habituation to any object type.

For each experiment, soiled cage bedding from cages containing four female mice (C57BL/6J strain) was used to label some objects with female odour. The objects to be labelled with female odour were placed in the bedding the day prior to each trial, around midday (12:00pm). For the experiments that lasted four days (Experiments 1, 3 and 4), halfway through each experiment (at the end of day 2), the bedding with female odour was replaced with bedding from a cage containing a second group of control females of the same strain. For the experiments that lasted only 2 days (Experiments 2, 5 and 6), the bedding remained the same throughout each experiment, but was changed before the start of the next experiment. The reason for this was that it was observed that the mice had a tendency to habituate to the smell after day 2 and using new bedding prevented this. Objects with female odour are here referred to as 'O+'. Copies of the same object but without odour are referred to as 'O-'. Objects that were never infused with odour are termed 'X-'. Y-mazes and objects were cleaned thoroughly with 70% ethanol and wiped with paper towels between trials with mice from different group cages, as well as at the end of each daily session.

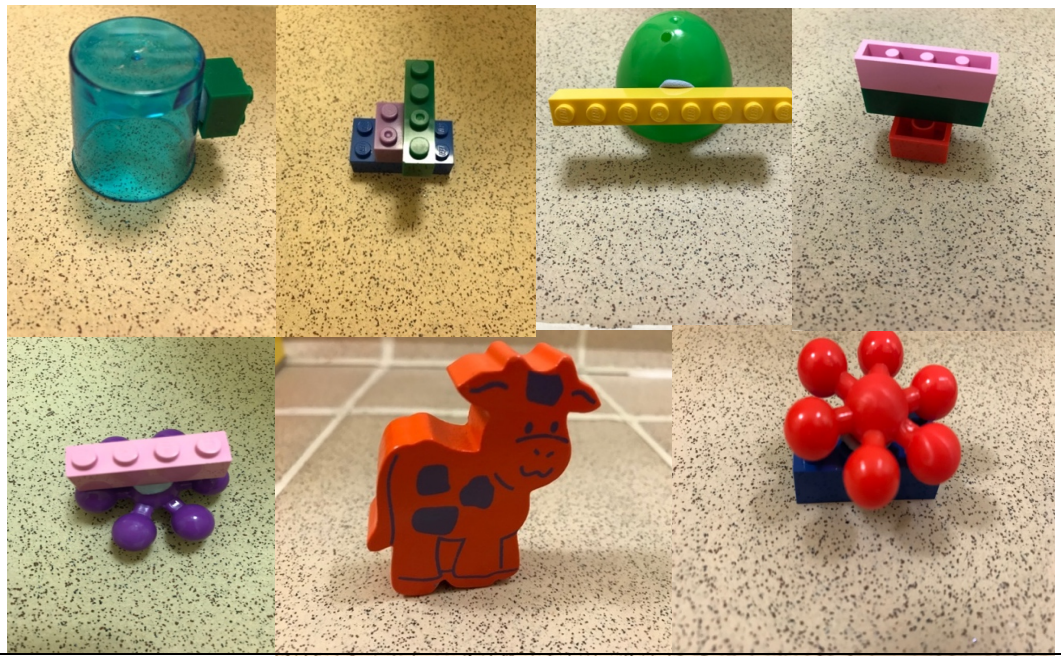

Figure 1. Examples for objects used in the study

Procedure. The tasks used in this study were a modified version of the classical NOR task (Berlyne, 1950). The procedure of each experiment is depicted in Figure 2. The study began with a familiarisation stage, during which the animals were handled for one minute on two consecutive days so that they became accustomed to the experimenter.

Habituation. After familiarisation, the mice were habituated to the testing apparatus and objects over a five-day period prior to Experiment 1. The first day of habituation consisted of a 10-minute cage group habituation session to the Y-mazes, in which mice from a given cage were placed together in one Y-maze, in the absence of objects. On the following day, the mice were exposed individually to the Y-maze for 10 minutes, again without objects. On the third day, the same steps from day 2 were repeated, but this time an O was present in either the left or right choice arm. On the fourth day, following the same steps as on day 3, each animal was exposed to another O-, but in the opposite arm to the one on day 3. The last day of habituation consisted of two exposures, this time with an O+ in either the left or right arm of the maze. The duration of exposure was 10 minutes and the interval between exposures was 5 minutes. During the 5-minute interval, the mice were placed in their holding cages and the O+s presented in the first exposure were replaced with different O+s for the second exposure. In addition, mice were habituated to O^a objects in either left or right arm.

Experimental stage. Following habituation, the mice were tested in six different experiments. Experiments 1, 3 and 4 were conducted on four consecutive days. Experiments 2, 5, 6 and 7b were conducted on two consecutive days. There were two experimental trials each day. The interval

between two experimental trials (ITI) was 5 minutes. During the ITI, the animals were placed in holding cages and the objects were replaced for the next trial. The particular object used in a given trial (O+, O-, X- or O^a), the order in which objects were presented and their locations in the maze (left or right choice arm) were randomised for each animal in each experiment. This randomisation ensured that each animal was exposed to a given object only in one experimental trial across the entire study. Each animal experienced the same number of O+, O-, O^a and X objects in each experiment. Apart from Experiment 1, each animal was exposed only to one O+ on each day and whether this was in the first or second trial of the day was counterbalanced. All of the experiments were performed consecutively by the same animals. Chronologically, the experiments were carried out in the following order: Experiment 1, Experiment 3, Experiment 4, Experiment 2, Experiment 5, Experiment 6, Experiments 7a and 7b. Thus, the mice were 14 weeks (3.5 months) old in Experiment 1, 16 weeks (4 months) old in Experiment 3, 19 weeks (almost 5 months) old in Experiment 4 and 29-30 weeks (around 7.5 months) old in Experiments 2, 5, 6 and 7a and 7b.

Experiment 1. This experiment consisted of eight trials in total per animal. Trials included one exposure to a single object, either O+ or O-. The duration of each trial was one minute (see row 1 of Fig. 2).

Experiment 2. This experiment was composed of four trials per animal. Each trial included an initial exposure to O- for one minute (the 'study phase'), either in the left or the right arm of the maze, followed by an exposure either to O- or O+ for 3 minutes (the 'test phase'; see row 2 of Fig. 2).

Experiment 3. This experiment included eight trials in total per animal. Each trial included a study phase, where animals were exposed to O- for one minute, either in the left or the right arm of the maze. The location of O- in the study phase is referred to as the 'familiar' location. The other location – the arm that was empty during the study phase – is referred to as the 'novel' location. During the test phase animals were exposed to both O- and O+ for 3 minutes. The O+ was always placed in the 'novel' location (see row 3 of Fig. 2).

Experiment 4. This experiment was identical to experiment 2, except that in the test phase O+ was in a familiar location (see row 4 of Fig. 2).

Experiment 5. This experiment was composed of four trials in total per animal. Each trial included a study phase, where animals were exposed to O- for one minute, either in the left or the right arm of the maze. The location of O- in the study phase is referred to as the 'familiar' location. The other location – the arm that was empty during the study phase – is referred to as the 'novel' location. During the test phase animals were exposed to both O+ and X- (an entirely novel object) for 3

minutes. The O+ was always placed in the 'novel' location (see row 5 of Fig. 2).

Experiment 6. This experiment was identical to experiment 5, except that O+ in the test phase always occupied a familiar location (see row 6 of Fig. 2).

Experiment 7a. In order to ensure that the mice were to some extent attracted to almond odour, we tested the preference of mice for almond odour in a four-trial-per-animal experiment, where mice were simultaneously exposed to two filter papers, one without any odour and the other infused with almond smell, at randomly determined locations in the Y-maze (left or right arm). To label the almond-odour paper with almond smell, we used a cotton-tipped applicator dipped in pure almond oil (100% concentration, by Atlantic Aromatics, Bray, Co.Wicklow, Ireland) and then scrubbed it on a small piece of filter paper.

Experiment 7b. In this experiment, O+ in the test phase was always placed at a familiar location and the O^a occupied a novel location (see row 7 of Fig. 2). The number of trials and the way the experiment was conducted was identical to Experiments 5 and 6. For labelling the objects with almond odour, we scrubbed O objects with cotton-tipped applicators dipped in pure almond oil (100% concentration, by Atlantic Aromatics, Bray, Co.Wicklow, Ireland), thus obtaining O^as; in addition, in order to remove the oiliness from these objects which could have led to a possible bias in attention capture (arising from a difference in texture between O+ and O-), the latter were also gently wiped with paper towel before being placed in the Y-mazes.

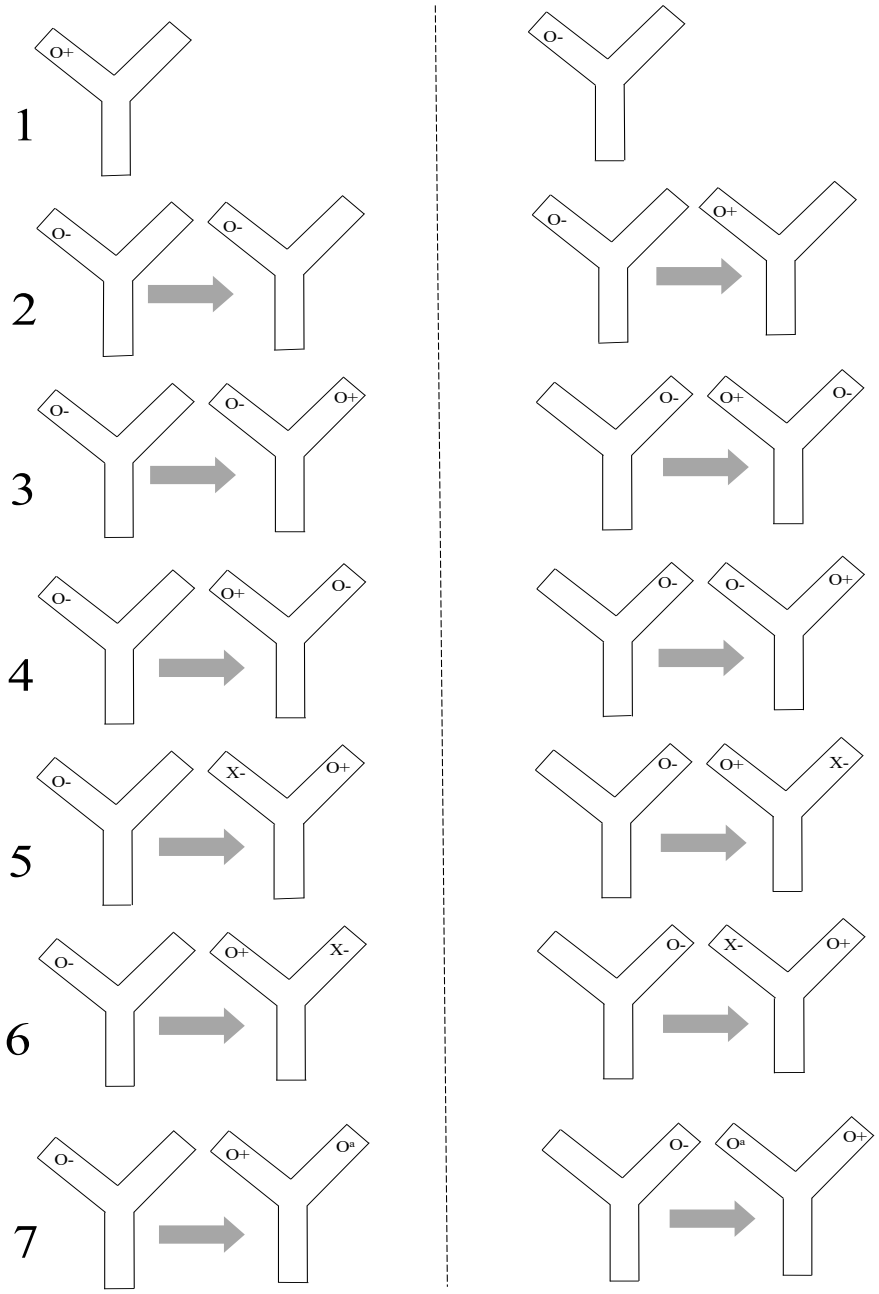

Figure 2. Experimental design.

Trial types in experiments 1-7 are illustrated (one experiment in each row). O+: female-mouse-odour-infused object. O-: odour-neutral object. X-: novel object, never infused with odour. O^a: almond-odour-infused object. Different copies of objects were used in two-phase experiments (Experiments 3-7).

Data analysis. Exploratory behaviour was recorded with video cameras and subsequently, object exploration time for each object was scored using the Novel Object Timer software (Jack Rivers-Auty; Novel Object Recognition Task Timer, 2015). The animal was considered to be exploring an object when its nose was within 2cm of the object and directed at the object. Sitting next to the object or climbing on top of the object was not regarded as exploratory behaviour. Each trial was scored twice for accuracy and the average of the two scorings taken as the object exploration time per trial. The mean exploration time of O+, O-, O^a and X- was obtained by averaging all trials with these objects for each animal.

The displacement index (D2), used to assess object preference from Experiments 3 onwards, was calculated using the formula: $D2 = (T_{O+} - T_{O-}) / (T_{O+} + T_{O-})$, where T_{O+} is the mean exploration time of O+ objects and T_{O-} is the mean exploration time of O objects. The values for this index are bound within a range of -1 and 1; positive D2 values indicated preference for O+, while negative values signified preference for O- and a value of 0 signified no preference (Burke, Wallace, Nematollahi, Uprety, & Barnes, 2010; Oliveira, Hawk, Abel, & Havekes, 2010).

The differences in total exploration time of O+, O-, O^a and X- were analysed with paired t-tests (two-tailed). D2 values were analysed with one-sample t-tests. In Experiments 3-4, we also investigated the effect of experiment day, using a repeated-measures 2 (Object type: O+, O-) x 4 (day: 1-4) ANOVA. Statistical tests were performed in GraphPad Prism 8.

Results

Experiment 1: Novel objects O+ vs. O-

The total time animals spent exploring O+ was significantly higher than the total exploration time for O- ($t(5)=4.11$, $p=0.0092$) as illustrated in Figure 3 (left panel). This finding demonstrates that when both O+ and O- are novel, the former attracts more attention. Two animals were excluded from the analysis of Experiment 1 due to a counterbalancing error.

Experiment 2: Familiar objects O+ vs. O-

The total object exploration time in Experiment 2 (Fig. 3 right panel) was significantly higher for O+ than O- ($t(7)=3.67$, $p=0.008$). This finding demonstrates that when both O+ and O- are familiar, the former attracts more attention.

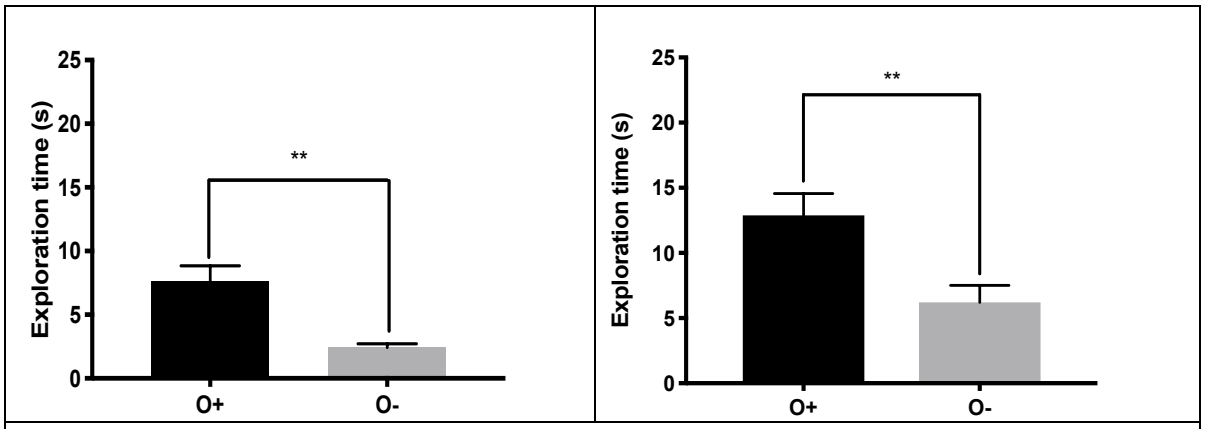

Figure 3. Exploration of single objects in Experiments 1 and 2.

Left: *Results of Experiment 1: Novel O+ vs. Novel O-.* ***Right:*** *Results of Experiment 2: Familiar O+ vs. Familiar O-. Bar graphs represent object exploration times (in seconds) averaged across animals. Data are presented as means ± SEM. Statistical significance is expressed with ** (p≤0.01).*

Experiment 3: Competition between O+ in a novel location and O- in a familiar location.

Figure 4 shows that the total exploration time for O+ was significantly higher than that for O- (t(7)=6.99, p=0.0002). Additionally, animals demonstrated a significant preference for O+ over O-, as indicated by D2 value, which was significantly higher than zero (t(7)=9.33, p<0.0001). Object exploration time was analysed across experimental days for any effect of day or interaction between object type and day. A repeated-measures two-way-ANOVA test found that there was a significant effect of object type (F(1,7)=47.84, p<0.001). While numerically this difference diminished across days, neither the effect of day (F(3,21)=2.93, p=0.06), nor the interaction (F(3,21)<1, p= 0.53) were significant.

Experiment 4: Competition between O+ in a familiar location and O- in a novel location.

The total exploration time of O+ was significantly higher than that of O- (*t*(7)=3.48, *p*=0.01; Figure 4). The D2 value (Figure 4), indicating the preference for O+ over O-, was significantly higher than zero (t(7)=3.67, p=0.008). Object exploration time was analysed across experimental days for any day effect or interaction between object type and day. Replicating the above results, there was a significant effect of object type (F(1,7)=12.02, p=0.01), as determined by a two-way-ANOVA test. As in the previous experiment, here the effect of day (F(3,21)=2.24, p=0.11) and the interaction (F(3,21)=1.13, p=0.36) were not significant.

At the end of the third experiment, it was interesting to determine if the mice had higher preference for O+ placed in a novel location than for O+ in a familiar location. The overall D2 values from experiments 3 and 4 were statistically compared with a Student's paired t-test. As illustrated in Figure

4, the D2 value for O+ in a novel location was significantly greater than that for O+ in a familiar location (t(7)=2.32, p=0.027), indicating that location novelty increased the motivational value of O+. However, since the D2 values were from two separate experiments, it is important to take into account possible confounds arising from a counter effect of habituation. Since Experiment 4 followed Experiment 3, animals might have been less motivated to explore the objects in the former than in the latter.

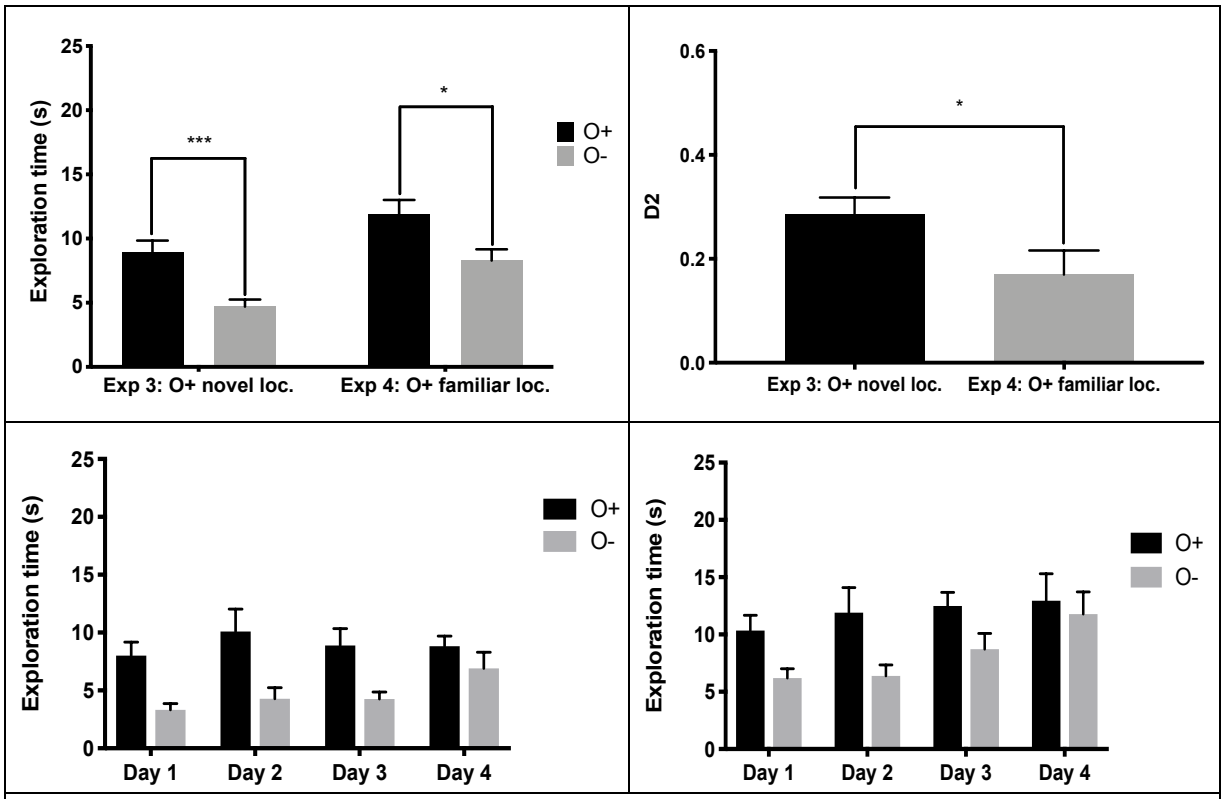

Figure 4. Results of Experiments 3 and 4.

Top left: Object exploration time in Experiments 3 and 4. *Means of object exploration time (seconds) were calculated by averaging across all animals.*

Top* right: *Effect of location familiarity on odour preference. *Mean D2 (discrimination index) value was obtained as the average of the D2 values from all animals.*

Bottom: Daily object exploration in Experiment 3 (Left) and 4 (Right). *Means of object exploration time (seconds) were obtained by averaging across all animals for each experimental day. The bar graphs represent means ± SEM. Statistical significance is expressed as ns (p>0.05), * (p≤0.05) or *** (p≤0.001).*

Experiment 5: Competition between O+ in a novel location and X- in a familiar location.

As shown in Figure 5, the total object exploration time in Experiment 5 was significantly higher for O+ than for X (t(7)=5.63, p=0.0008). A one sample t-test showed that the D2 value was significantly higher than zero, indicating a preference for O+ over X (t(7)=4.92, p=0.0017).

Experiment 6: Competition between O+ in a familiar location and X- in a novel location.

The total object exploration time in Experiment 6 was higher for O+ than for X-, however, the

difference was not statistically significant (t(7)=1.8, p=0.1158, Figure 5). The D2 value in this experiment was also not significantly higher than zero, suggesting no significant preference for O+ over X- (t(7)=2.023, p=0.0828).

Additionally, the results from Experiment 5 and Experiment 6 were compared in order to determine the effect of location familiarity and object type (novel identity or odour-infused) on exploration time and object preference. The same caveats hold for this comparison across experiments as for the one across Experiments 3 and 4. A repeated-measures two-way-ANOVA test found that there was a significant effect of location (F(1,7)=19.23, p=0.003) with a preference for the novel object, as well as of object type (F(1,7)=11.68, p=0.011), but no significant interaction (F(1,7)=1.59, p=0.246). It is difficult to interpret these results conclusively as indicative of additive or sub-additive effects, given the lack of counterbalance between experiments and potential effects of habituation.

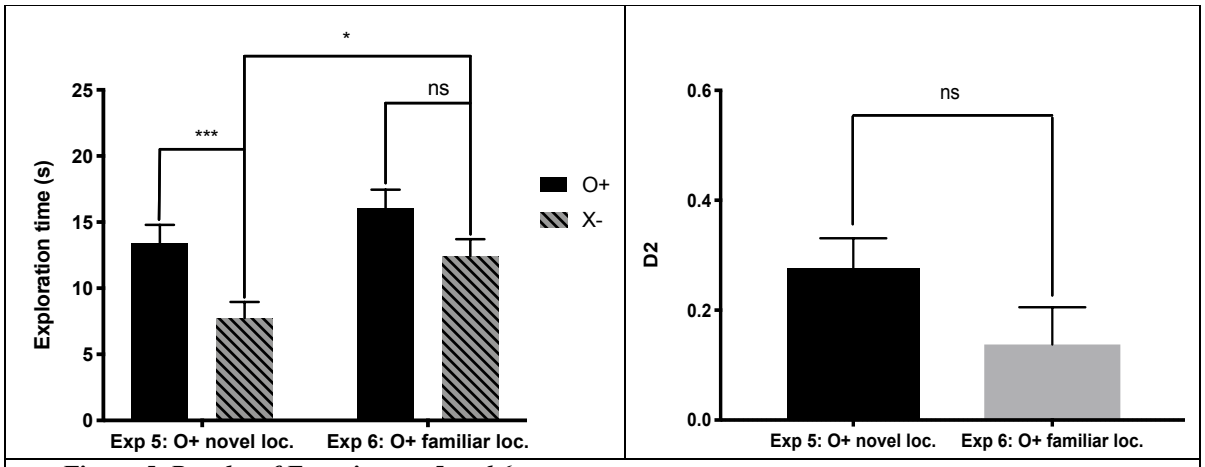

Figure 5. Results of Experiments 5 and 6.

Left: Effect of object identity and location familiarity on exploration time. *Means of object exploration time (seconds) were calculated by averaging across all animals. Bar graphs represent object exploration times (in seconds) averaged across animals.*

Right: Effect of object identity and location familiarity on object preference. *Mean D2 (discrimination index) value was obtained as the average of the D2 values from all animals. Data are presented as means ± SEM. Statistical significance is expressed as ns (p>0.05),* (p≤0.05) or *** (p≤0.001).*

In Experiments 5 and 6, it was also interesting to observe the choice the animal made when it had to decide which object to explore first (O+ or X-); this is referred to as *first object choice*. A binomial test revealed that there was not enough evidence to reject the null hypothesis, according to which animals were equally likely to explore either object (p=0.1402 in Experiment 5, p=0.2153 in Experiment 6).

Experiment 7a was necessary to investigate if mice are able to detect the smell of almond and, moreover, if they find this smell attractive. Figure 6 shows that the total exploration time of filter

papers with almond odour was significantly greater than the exploration time of an odour-free filter paper (t(7)=2.9, p=0.0229). The D2 value, which was found to be significantly higher than zero (t(7)=3.5, p=0.0101), confirms the preference of mice for almond odour compared to no odour.

Experiment 7b: Competition between O+ in a familiar location and O^a in a novel location.

The overall exploration time for O+ was significantly higher than that for O^a (t(7)=7.5, p=0.0001) and the D2 value was significantly larger than zero (t(7)=11.5, p<0.0001, Figure), indicating preference for O+ over O^a.

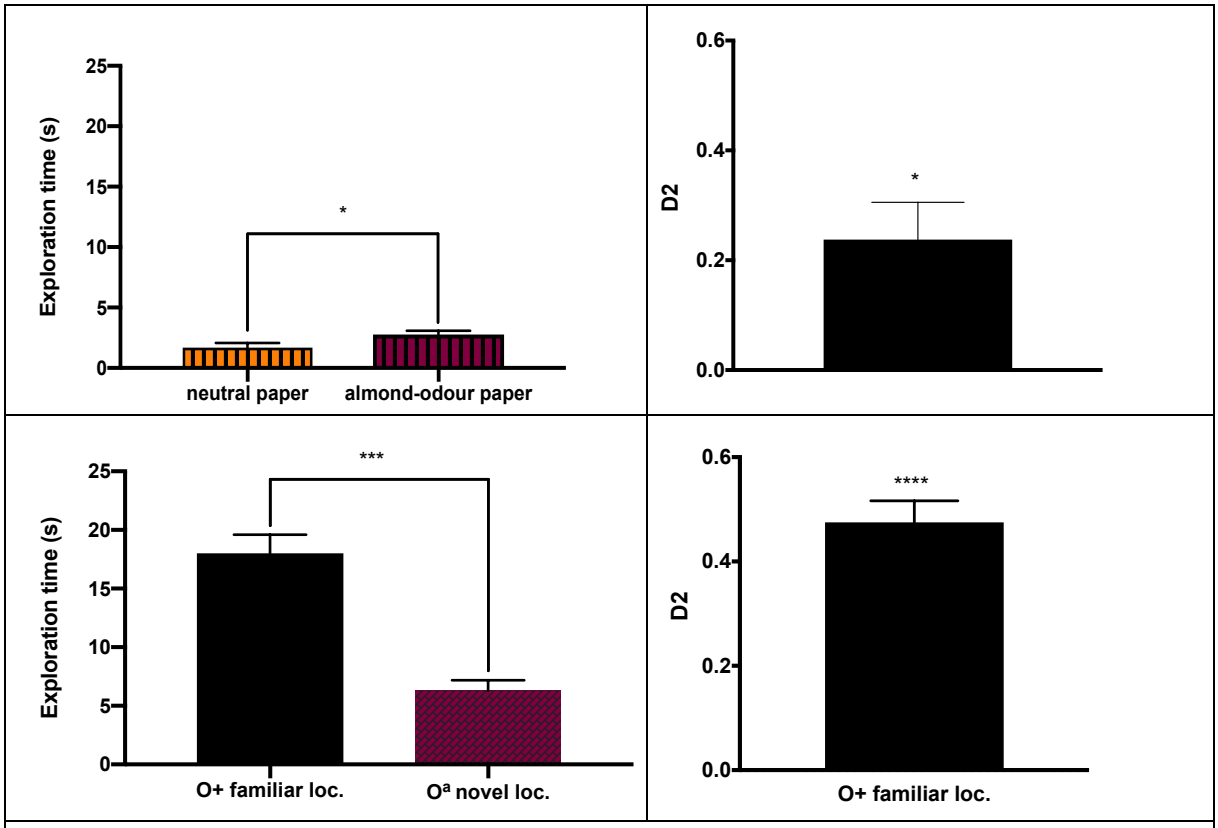

Figure 6. Results of Experiment 7.

Top left: Effect of odour on exploration time in Experiment 7a. *Means of object exploration time (seconds) were calculated by averaging across all animals. Bar graphs represent exploration times (in seconds) averaged across animals.*

Top right: Odour preference in Experiment 7a. *Mean D2 (discrimination index) value was obtained as the average of the D2 values from all animals. Data are presented as means ± SEM. Statistical significance is expressed as * (p<0.05).*

Bottom left: Effect of odour on exploration time in Experiment 7b. *Means of object exploration time (seconds) were calculated by averaging across all animals. Bar graphs represent object exploration times (in seconds) averaged across animals.*

Bottom right: Effect of odour on object preference in Experiment 7b. *Mean D2 (discrimination index) value was obtained as the average of the D2 values from all animals. Data are presented as means ± SEM. Statistical significance is expressed as *** (p≤0.001) or **** (p≤0.0001).*

Discussion

Evidence for VMAC from sensory domains outside vision is sparse, despite abundant research on different sensory modalities involved in bottom-up and top-down attention processes (Spence, 2010). The reason for this is that the initial identification of VMAC was for visual cues and since then, the scientific focus has been on analysing how learnt value affects visual attention (Chelazzi et al., 2014; Failing & Theeuwes, 2014; Qi, Zeng, Ding, & Li, 2013). Extending the principles of VMAC to other sensory domains is essential for a more complex understanding of this attentional process and can help integrate current knowledge of the modulatory effects of learnt reward on sensory processing (Pantoja et al., 2007). In the study we report here, we investigated the attentional capture by an olfactory stimulus and the possibility of any cross-modal interference with visual stimulation by an object at a novel location or a novel object in the arena.

Previous studies have shown that female odour represents a positive arousing stimulus for laboratory male mice (Beny & Kimchi, 2014; Connor, 1972; Mackintosh, 1970). According to Beny and Kimchi (2014), sexually inexperienced (naïve) male mice display sexual behaviours towards female conspecifics and manifest aggression towards other male mice. Connor (1972) demonstrated that pheromones found in urine are responsible for these dimorphic behaviours. In his experiments, male mice displayed milder aggressive behaviours towards male intruders smelling of female urine and behaved aggressively towards females swabbed with male urine. These behaviours are genetically determined and, therefore, do not require prior learning. The only experience these laboratory mice had with female odours was during weaning, in the presence of their mothers, after which they were isolated from female conspecifics.

In line with these observations, the results from our Experiments 1 and 2 support the conclusion that male mice pay significantly more attention to O+ than O-. In general, in these experiments, there seems to be longer exploration of familiar objects compared to novel ones, which might be explained be a slight neophobia in the mice. Taken together, these experiments confirmed our hypothesis that female odour captures more attention than an odourless object. These experiments ensured that our mice displayed behaviours as expected, based on the aforementioned literature, so we were able to proceed to the next stages of the study.

The following aims were to elucidate how much attention odour would capture when the location of O+ was either novel or familiar. Previous studies have already established that under normal conditions, adult rats show preference for an object at a novel location compared to an identical object at a previously experienced location (Aggleton, Albasser, Aggleton, Poirier, & Pearce, 2010; Barker & Warburton, 2011; Ennaceur et al., 1997). Therefore, it was not surprising that in Experiment 3, O+

at a novel location attracted more attention than an O- at a familiar location, since both its odour and location provided O+ with more motivational significance than O-. Interestingly, in Experiment 4, where O+ at a familiar location competed with O- at a novel location, O+ still attracted more attention. This represents a notable finding, as it shows that female odour 'wins' over a previously known arousing factor (location novelty) in the amount of attention captured. In a human study of auditory attention, Anderson (2016) demonstrated that VMAC by sounds previously associated with a reward interfere with a visual task and compete with the visual representation of stimuli, reflecting cross-modal stimulus competition bias by VMAC. Our study shows that, at least in mice performing a NOR task, a positively stimulating odour outcompetes a visual stimulus (location novelty) for attention, thus extending the findings from humans to animals and also to a different sensory domain.

At first glance, the observation that O+ at a novel location attracts more attention than O+ at a familiar location might seem intuitive: in the first case, O+ consists of two motivational stimuli – odour and location novelty, while in the second case O+ only has the odour. However, this also emphasises an aspect worth taking into consideration – the fact that multiple stimuli can act in combination to influence attention. Studies focusing on episodic memory have demonstrated that rats and mice form integrated representations of three distinct object features: its identity, location and the context in which it was experienced. Being able to associate these separate components allows the animal to achieve a complex representation and record of environmental experiences, and this has been termed 'episodic-like memory' in rodent models (Davis, Eacott, Easton, & Gigg, 2013; Eacott, 2004). In light of this work, the interpretation of how O+ at familiar location versus O+ at novel location affects attention allocation could be further extended. The combination of odour and location provides the animal with more detailed information about the object and, thus, it attracts more attention than either odour or location alone. This suggests that odour can act not only on its own, but also as a component of a stimulating context to modify the degree of attention allocation, thus influencing other cognitive processes (e.g., episodic memory) in an additive manner.

Statistically, there was no day effect on the exploration time of O+ and O- in Experiments 3 and 4. However, the daily means of exploration time indicate that there was a tendency for the attention capture by O+ to decline across trials. This might be due to the male mice learning over the first three trials that if they encounter female olfactory cues, this does not predict the availability of the female mice, so the female odour starts to lose attentional allocation. This observation should be considered in future behavioural studies using odours, particularly if such studies involve several trials. In our study, using odour from different females after four consecutive trials was an attempt to avoid habituation to odour.

Once we were able to determine that odour elicits more attentional capture than location novelty, the next logical step was to study attention allocation to odour when competing with another powerfully arousing stimulus – novel identity. The motivational value of novel identity has been the premise of many studies using the NOR task, in which rodents are expected to pay more attention to the novel rather than the familiar object. In our study, odour captured more attention than a novel object when the location of the former was novel, while the location of the latter was familiar (Experiment 5). If we assume that location is a visual stimulus, then odour in association with a visually arousing stimulus captures more attention than another visual stimulus known to be salient to rodents. However, in Experiment 6, when X- was placed at a novel location and O+ at a familiar location, odour could no longer 'win' over novel identity plus location in the degree of attention allocation. These findings suggest that, on their own, odour and object identity might have the same motivational significance to mice and their combination with other arousing stimuli can shift the balance in favour of one over the other.

Nevertheless, it is not yet clear how visual and olfactory stimuli interact to capture the attention of mice and whether the two kinds of stimuli are indeed equally motivational. A rather surprising observation in Experiment 5 was that, in a single case, a particular X- type attracted more attention than its O+ counterpart; this indicates that in some circumstances, visual cues elicit stronger effects on attention than olfactory cues. Le Pelley et al. (2016) argue that competition between a physically salient and a less salient cue can alter attention, which can in turn affect the degree of learning. Since both visual and olfactory cues convey important adaptive information to rodents, the question we might ask is what determines whether a certain visual or olfactory cue attracts more attention than other motivational stimuli present in the same environment. This question should motivate further research into object type preference in mice, as well as more comparisons between the effects of visual and olfactory cues on attention allocation.

A recent study in monkeys showed that for the visual system, novelty enhanced the motivational value of stimuli associated with a negative outcome, while for the reward system, the effects of novelty dissipated for such stimuli (Foley, Jangraw, Peck, & Gottlieb, 2014). This led the researchers to conclude that novelty acts on attentional mechanisms independent of reward to influence the processing of information and learning. In light of this finding, our experiments in mice could be interpreted not just in terms of competition between novelty and a reward-associated stimulus, but rather as evidence that reward and novelty are dissociable. In the future, it would be interesting to investigate in humans whether this distinction can be made at both psychological and neurobiological levels, especially since, contrary to this theory, prior research on animals has suggested that the effects of novelty can be explained in terms of reward (Horvitz, 2000; Kakade & Dayan, 2002; Laurent, 2008).

Several studies have demonstrated that the value of a particular stimulus feature (e.g., colour) in predicting reward results in more attention being allocated to the same or similar features (Kalish & Kruschke, 2000; Lawrence, Sahakian, Rogers, Hodges, & Robbins, 1999; Sutherland & Mackintosh, 1971). In our study, male mice were likely to evaluate female odour as an endogenously highly motivational stimulus. We are still uncertain as to whether naïve males consider female odour to be reminiscent of their mothers and, thus, have a predictive value acquired through learning. In the future, it would be useful to compare the degree of attention allocation to female odours with that to odours or other stimuli that are predictive of an outcome (preferably a rewarding outcome, since female odour is considered a positively arousing stimulus due to its effects on reproductive behaviours).

In our study, mice clearly showed more interest in a filter paper infused with almond smell than in an odour-free filter paper. As expected, there was an observable trend of the overall exploration time to decrease over the course of the four trials, which is in line with the findings of Rattazzi, Cariboni, Poojara, Shoenfeld, & D'Acquisto (2015), who reported that mice habituated to the odours after the first exposure, since the odour exploration time was significantly reduced in the second and third exposures compared with the first exposure.

Rattazzi, Cariboni, Poojara, Shoenfeld, & D'Acquisto (2015) used a 100-fold dilution of almond extract (10µl almond extract to 990µl distilled water) and the solution was prepared in the morning of the same day of the test. In the present study, almond-odour infused filter papers and O^a objects were also prepared on the day of each trial, but we did not use any dilutions (O^a objects had been labelled with 100%-concentrated almond oil). Given that the potency of almond oil in our experiment was likely higher than that used by above-mentioned authors, almond odour could have 'trumped' female odour in animals' attention capture. This was, however, not the case – mice consistently showed significantly higher exploration time and preference for O+ in Experiment 7. This observation was very interesting, as it not only confirmed that mice are more attracted to female odour than to a non-social odour (which was already well-established in the literature), but it showed that this holds true, even when almond odour is intense and found at a novel location. Experiment 7 represents a very important addition to our study, because with it we were able to compare the degree of attention allocation to female odour with that to another olfactory stimulus with lesser motivational significance.

One explanation that could have accounted for the very high preference of mice for O+ compared with O^a was that, in fact, the high concentration of almond oil resulted in the odour of O^a being aversive to the mice. According to (Saraiva et al., 2016), some odours that are attractive at a low concentration can become aversive in high concentrations. In our Experiment 7, however, we were

able to determine whether the mice were attracted or repulsed by the almond smell by looking at the video recordings. Mice did not display avoidance behaviour toward O^a objects; they not only sniffed the O^as multiple times upon their first discovery of such object in one of the Y-maze's arms, but they also returned to this object several times during the 3-minute test. Considering that the Y-maze contains three arms and that in Experiment 7, one arm was always object-free, and another arm contained a highly attractive odour (O+), the animal could have easily avoided O^a by never returning to the respective arm. Clearly, mice did not find O^as aversive, but they showed a distinct preference for O+s.

In summary, the present study used object exploration measures to quantify the degree of attention allocation by male mice to object novelty and/or female odour. Initial experiments demonstrated that in the absence of other arousing features, objects with female odours capture more attention than an odour-neutral object. These results agree with previous research showing that under laboratory conditions, sexually isolated male mice are aroused by the odour of female conspecifics. The study further demonstrated that odour 'wins' over location novelty in the degree of attention allocation and that its motivational value is even greater in combination with location novelty. This supports the conclusion that odour interacts with other arousing stimuli to form arousing contexts. Female odour was able to capture more attention than a novel object, but only when combined with location novelty, suggesting that the additive effects of visual and olfactory cues on attention exceed those of a single strongly arousing stimulus. Finally, female odour attracted more attention than a mildly attractive odour (low in motivational significance), suggesting that mice are able to form emotionally-charged memories that are different from memories associated with other stimuli. These experiments contribute to the understanding of the effects of female odour on value-modulated attention capture and provide a reliable protocol to quantify attention allocation in mice. The findings obtained here should encourage future research to use odour in investigating the influence of emotional arousal on attention and memory.

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