



## Special Issue: Biochemistry &amp; Animal Communication

## Innate and learned aspects of pheromone-mediated social behaviours



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## ARTICLE INFO

## Article history:

Received 31 March 2014  
 Initial acceptance 20 May 2014  
 Final acceptance 4 September 2014  
 Available online 3 October 2014  
 MS. number: 14-00269R

## Keywords:

associative learning  
 dopamine  
 innate behaviour  
 main olfactory epithelium  
 neural pathway  
 pheromones  
 reproductive behaviour  
 reward value  
 rodents  
 vomeronasal organ

All species perceive sensory stimuli from the environment through dedicated sensory modalities, and respond with appropriate behaviours designed to maximize fitness and reproductive success. In most mammalian species, information regarding sex, age and other species-specific social and reproductive characteristics is conveyed by pheromones, which are detected by the vomeronasal and olfactory systems. Traditionally, pheromone signals have been thought to possess intrinsic rewarding meanings and to trigger 'innate' hardwired social behavioural responses. In contrast, odorants are considered to possess mostly neutral reward value, but may induce approach or avoidance behaviours as a result of experience or through conditioning following pairing with stimuli that possess intrinsic rewarding properties. This review describes studies demonstrating that innate behavioural responses, with particular emphasis on reproductive responses mediated by pheromonal signals, are actually flexible and substantially influenced by past experience and associative learning. These attributes allow the animal to assign new motivational incentives to pheromones associated with social and reproductive behaviours, thus providing adaptive ability to cope with unique changes in internal and external environmental conditions. We argue that responses to pheromones are far more easily modified by experience than would be expected from hardwired innate responses, and that the behaviours they elicit are chiefly plastic and sensitive to modification throughout life by sensory-mediated emotional experience.

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*All behaviour is a reaction... to a certain extent, dependent on external stimulation...[and]... is spontaneous in so far as it is also dependent on internal causal factors, or motivational factors, responsible for the activation of an urge or drive.*

**Nikolaas Tinbergen (Tinbergen, 1969, p. 15)**

The behaviour of all living entities including insects (Dudareva & Pichersky, 2006), rodents (Davies & Krebs, 1997) and primates (Cartwright, 2000) is driven by sensory information that is acquired from the external environment. Such biotic and abiotic sensory cues, detected via specialized sensory mechanisms adapted to the unique niches of each species (Alcock, 2013; Lorenz, 1935), play a key role in behavioural decisions essential to the animal's reproductive success and survival (Davies & Krebs, 1997).

The interpretation of these stimuli to convey meaning that will guide the animals' behavioural decisions is largely dependent on that individual's internal state (Mannella, Gurney, & Baldassarre, 2013). According to the hydraulic model of Lorenz, a behaviour is associated with an action-specific energy (drive/motivation),

described as a reservoir containing a fluid that accumulates until the animal encounters a specific external sensory stimulus. When the animal perceives such a stimulus, given the right motivational (internal) state, the stored energy is released, leading to the execution of a fixed action (innate) behavioural pattern (Lorenz, 1950). Thus, a given stimulus may trigger a maximal reaction in one motivational state but may have no effect or even trigger an opposite reaction in another (Sullivan, Landers, Yeaman, & Wilson, 2000; Tinbergen, 1969).

One of the main internal factors affecting an animal's motivational state and subsequent innate behavioural decisions is its unique hormonal profile, which depends, among other factors, on its age, reproductive state and past experience (Hastings, O'Neill, & Maywood, 2007). In rats, *Rattus norvegicus*, as in other mammals, the maternal motivation of females to suckle newborn pups has been shown to be dependent on changes in the milieu of peripheral hormones including oestradiol, progesterone (Bridges, 1984) and prolactin (Bridges & Ronsheim, 1990). In nulliparous females, the latency to initiate pup-caring behaviour seems to correlate with oxytocin levels in the central nervous system. It has been suggested that oxytocin release in the brain might be part of an array of neuroendocrine events, mediated by the pup's odours, that together determine the initial aversion to pups observed in nulliparous females (Fahrbach, Morrell, & Pfaff, 1984). Furthermore, in rodents, male copulatory behaviour and motivational aspects of

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sexual behaviour are critically dependent on steroid hormones (testosterone) secreted in adulthood. Castration diminishes the motivation of males to investigate sexual partners and engage in copulatory behaviour (Harding & McGinnis, 2003; Harding & Velotta, 2011), and eliminates their preference for oestrous female odours over male odours (Paredes, Lopez, & Baum, 1998; Stern, 1970). It has been suggested that steroid hormones facilitate the responses of sensory neurons to conspecific stimuli (such as sexually relevant odours), so that a given external stimulus will be more likely to elicit a sexual response (Hull et al., 1999).

Another key factor affecting the reaction of an animal to a specific stimulus, and particularly the motivation to initiate innate behavioural responses, is its past learning experience. A neutral external stimulus can acquire a positive reward value once the animal learns that it predicts the occurrence of a rewarding event. As a result of this 'associative learning', the formerly neutral stimulus can induce the activation of reward-related circuits in the brain (Brischoux, Chakraborty, Brierley, & Ungless, 2009; Matsumoto & Hikosaka, 2009; Mirenovic & Schultz, 1996) and elicit an 'approach' behavioural response (Berridge, 2000).

Reproductive behaviours, including courtship, mating, pup nursing and aggression, are conventionally classified as hardwired, genetically programmed innate behaviours (Brouette-Lahlou, Godinot, & Vernet-Maury, 1999; Chamero et al., 2007; Choi et al., 2005; Roberts et al., 2010), which arise independently of the animal's experience and environment and are distinct from acquired (learned) behaviours (Lehrman, 1953). In most mammals these reproductive behaviours are largely regulated by chemosignals, referred to as pheromones. Pheromones are believed to carry intrinsic positive or negative reward values that mediate the innate emotional responses to these chemical signals.

Male laboratory mice, *Mus musculus*, typically display strikingly different behaviours towards male and female conspecifics. Male intruders are usually viciously attacked, whereas female intruders are not attacked but instead are sexually mounted (Mackintosh, 1970; Scott & Fredericson, 1951). In an elegant set of behavioural assays it was demonstrated that these dimorphic behavioural responses are mediated mainly by pheromone signals secreted in urine and that they seem to be innate, requiring no prior learning (Connor, 1972). A sexually inexperienced (naïve) male that is isolated after weaning and introduced to a strange male will instigate an instinctive aggressive attack towards the intruder. When the naïve male is introduced to a male intruder swabbed with female urine (a major source of pheromones), it performs milder aggressive displays and attempts to mount it. However, when the male is introduced to a female swabbed with male urine, sexual behaviour towards the female is repressed and replaced with more forceful aggressive behaviour (Connor, 1972).

In contrast to the innate nature of pheromone action, numerous studies have demonstrated that the pheromone-mediated reproductive repertoire of behaviours is open to modifications through learning and past experience (Pfaus, Kippin, & Centeno, 2001). Modification through learning is evident both in goal-directed appetitive behaviours, in which the animal approaches and investigates the rewarding conspecific stimulus, and in consummatory aspects of reproductive behaviours (Argiolas & Melis, 2013).

This review focuses on the role of pheromone signals in regulation of the innate and learned aspects of reproductive responses. We discuss the integrative role of the main and the vomeronasal olfactory systems in mediating the innate and the learned rewarding properties of pheromonal signalling, as well as the neuroanatomical and the neurobiochemical basis underlying the rewarding effects of pheromones that shape reproductive behaviours.

## WHAT ARE PHEROMONES?

Pheromones are chemicals that have evolved as signals for communication between members of the same species (Wyatt, 2014). Chemical communication is ubiquitous across the animal kingdom, from insects (Wang & Anderson, 2010) through fish (Sorensen, Christensen, & Stacey, 1998) to mammals, including rodents and nonhuman primates (Stowers & Marton, 2005; Tirindelli, Dibattista, Pifferi, & Menini, 2009). In humans the existence of pheromonal communication is controversial (Doty, 2010), although several recent studies have demonstrated that human body secretions (Gelstein et al., 2011; Zhou & Chen, 2009) and two gender-specific human steroids, androstadienone and estratetraenol, might possess functional biological properties in conspecific communication (Grosser, Monti-Bloch, Jennings-White, & Berliner, 2000; Savic, Berglund, & Lindstrom, 2005; Zhou et al., 2014).

Pheromones are either single compounds or a combination of molecules in a precise ratio (Wyatt, 2014), which are emitted to the external environment by one individual (the releaser) and may elicit a variety of behavioural and endocrinological responses in another individual that detects them (Liberles, 2014). In mammals, specific pheromones convey information about the releaser, including its species, age, sex (Cheetham et al., 2007; He, Ma, Kim, Nakai, & Yu, 2008; Isogai et al., 2011; Leinders-Zufall et al., 2004; Meeks, Arnson, & Holy, 2010), reproductive/endocrine state, familiarity and social status (Ben-Shaul, Katz, Mooney, & Dulac, 2010; Bergan, Ben-Shaul, & Dulac, 2014; Hurst & Beynon, 2004). Pheromone molecules are released from a wide range of body secretions including urine (Beynon & Hurst, 2004), preputial gland secretions (Ponmanickam et al., 2013), tears (Gelstein et al., 2011; Haga et al., 2010), saliva (Talley, Laukaitis, & Karn, 2001) and mammary gland secretions (Charra et al., 2012; Schaal et al., 2009).

In most mammals, pheromonal cues and odorants are detected by two distinct nasal chemosensory structures, the main olfactory epithelium (MOE) and the vomeronasal organ (VNO) (Munger, Leinders-Zufall, & Zufall, 2009). In rodents, the MOE expresses about 1000 G-protein-coupled olfactory sensory receptors that are mostly devoted to detection of volatile odours such as natural odours and food signatures, as well as avoidance/fear-eliciting odours (for example, predator or spoiled food odour; Kobayakawa et al., 2007). The VNO expresses about 300 G-protein-coupled vomeronasal sensory receptors. These receptors, which detect both volatile and nonvolatile pheromones, play a critical role in identifying sex- and species-specific chemical cues and in mediating mating, territorial aggression, defensive responses to predators and associated endocrine changes (Chamero, Leinders-Zufall, & Zufall, 2012). Some vomeronasal sensory neurons have been found to harbour members of the formyl peptide receptor family, which seem to allow chemosignals associated with pathogen- and inflammation-related compounds to be detected (Liberles et al., 2009; Riviere, Challet, Fluegge, Spehr, & Rodriguez, 2009). Two additional known chemosensory structures in the nasal cavity of rodents are the Grüneberg ganglion neurons and the septal organ of Masera (Giannetti, Saucier, & Astic, 1992; Grüneberg, 1973). Both are part of the MOE and are considered to be responsible for mediating specific olfactory behaviours, such as detection of alarm pheromones by the Grüneberg ganglion neurons (Brechtbuhl, Klaey, & Broillet, 2008; Table 1). The septal organ predominantly expresses a small subset of olfactory receptors that respond broadly to general odorants whose behavioural function is not yet understood (Ma et al., 2003).

Pheromonal cues are characterized by wide chemical and functional variability and are often classified according to two distinct criteria (Table 1). First, pheromonal ligands are classified by

**Table 1**  
Intrinsic reward value of pheromonal signals

| Ligand   | Species/Sex (source)     | Effect  | Intrinsic reward value           | Source   |
|--|--------------------------|---|----------------------------------|--|
| <b>Vomer nasal organ (VNO)</b>   |                          |   |                                  |  |
| Small molecules  |                          |   |                                  |  |
| 2-heptanone  | Mice                     | Extend female oestrous cycle                                      | Neutral                          | Brennan & Zufall, 2006; Zufall & Leinders-Zufall, 2007   |
| 6-hydroxy-6-methyl-3-heptanone   | Male mice                | Accelerate puberty in females                                     | Neutral                          | Del Punta et al., 2002; Novotny, 2003  |
| $\alpha$ - and $\beta$ -farnesene  | Male mice                | Accelerate puberty<br>Attract females<br>Signal dominant males    | Neutral<br>Positive*<br>Negative | Brennan & Keverne, 2004; Leinders-Zufall et al., 2000<br>Jemiolo et al., 1991<br>Novotny, Harvey, & Jemiolo, 1990                  |
| Dehydro- <i>exo</i> -brevicomin & 2-( <i>sec</i> -butyl)-4,5-dihydrothiazole | Male mice                | Promote aggression  | Positive <sup>†</sup>            | Brennan & Keverne, 2004; Novotny, Harvey, Jemiolo, & Alberts, 1985   |
| Isobutylamine  | Male mice                | Induce Whitten effect in females<br>Accelerate puberty in females | Neutral<br>Neutral               | Jemiolo et al., 1986; Leinders-Zufall et al., 2000<br>Del Punta et al., 2002; Nishimura, Utsumi, Yuhara, Fujitani, & Iritani, 1989 |
| 2,5-dimethylpyrazine   | Female mice              | Delay puberty in females  | Neutral                          | Baxi, Dorries, & Eisthen, 2006; Novotny, 2003  |
| 17 $\beta$ -diol disulphate (E1050)  | Female mice              | Signal oestrous females   | Positive                         | Haga-Yamanaka et al., 2014; Isogai et al., 2011; Nodari et al., 2008   |
| Corticosterone-21 sulphate (Q1570)   | Female mice              | Signal stressed females   | Negative                         | Celsi, D'Errico, & Menini, 2012; Isogai et al., 2011; Nodari et al., 2008  |
| Proteins and peptides  |                          |   |                                  |  |
| MHC class 1 peptides   | Mice                     | Bruce effect  | Neutral                          | Leinders-Zufall et al., 2004; Zufall & Leinders-Zufall, 2007   |
| Peptides associated with inflammation (CRAMP, uPAR, SAA)                     | Mice                     | Signal unhealthy conspecifics                                     | Negative                         | Kavaliere, Cholieris, Agmo, & Pfaff, 2004; Riviere et al., 2009; Stowers & Logan, 2010   |
| Major urinary proteins (MUPs)  | Male mice                | Promote aggression  | Positive                         | Chamero et al., 2007   |
| Exocrine gland-secreting peptide 1 (ESP1)                                    | Female mice              | Increase female receptivity                                       | Neutral                          | Haga et al., 2010; Kimoto, Haga, Sato, & Touhara, 2005   |
| ESP22  | Juvenile mice            | Inhibit sexual behaviour  | Negative                         | Ferrero et al., 2013   |
| Dodecyl propionate   | Rat pups                 | Promote approach and maternal anogenital licking                  | Positive                         | Brouette-Lahlou et al., 1999; Mucignat-Caretta et al., 2012; Schaal, 2010  |
| MUP 13   | Rats                     | Fear response   | Negative                         | Papes et al., 2010   |
| MUP Feld4  | Cats                     | Fear response   | Negative                         | Papes et al., 2010   |
| <b>Main olfactory epithelium (MOE)</b>                                       |                          |   |                                  |  |
| Small molecules  |                          |   |                                  |  |
| Isoamylamine   | Mice                     | Accelerate puberty  | Neutral                          | Liberles & Buck, 2006; Nishimura et al., 1989  |
| (Methylthio)methanethiol (MTMT)  | Male mice                | Attract females   | Positive <sup>†</sup>            | Lin et al., 2005; Zufall & Leinders-Zufall, 2007   |
| Trimethylamine   | Male mice                | Attract mice  | Positive                         | Li et al., 2013; Liberles & Buck, 2006   |
| 2-methylbut-2-enal (2MB2)  | Female rabbits           | Promote nipple search and suckling                                | Positive                         | Schaal et al., 2003; Zufall & Leinders-Zufall, 2007  |
| 2,5-dihydro-2,4,5-trimethylthiazoline (TMT)                                  | Foxes                    | Fear response   | Negative                         | Buron et al., 2007; Staples et al., 2008   |
| $\beta$ -phenylethylamine  | Carnivores (e.g. feline) | Fear response   | Negative                         | Dewan, Pacifico, Zhan, Rinberg, & Bozza, 2013; Ferrero et al., 2011  |
| Proteins and peptides  |                          |   |                                  |  |
| MHC class 1 peptides   | Mice                     | Enhance attractiveness of females of different strains            | Positive                         | Spehr et al., 2006; Zufall & Leinders-Zufall, 2007   |
| <b>Grüneberg ganglion (GG)</b>   |                          |   |                                  |  |
| Small molecules  |                          |   |                                  |  |
| 2-( <i>sec</i> -butyl)-4,5-dihydrothiazole (alarm pheromone)                 | Mice                     | Fear and anxiety responses  | Negative                         | Brechbuhl et al., 2008; Brechbuhl et al., 2013; Kikusui et al., 2001   |

\* Only at high concentrations.

† Tested on experienced mice.

their molecular features as small volatile molecules such as the rabbit mammary pheromone 2-methylbut-2-enal (Schaal et al., 2003), male-specific mouse pheromones such as (methylthio) methanethiol (Lin, Zhang, Block, & Katz, 2005), or as sulphated steroids (Meeks et al., 2010; Nodari et al., 2008) or nonvolatile peptides such as the exocrine gland-secreting peptide 1 in mice (Haga et al., 2010), the protein pheromone darcin (Roberts, Davidson, McLean, Beynon, & Hurst, 2012; Roberts et al., 2010) and major histocompatibility complex (MHC) class I molecules (Leinders-Zufall et al., 2004). Furthermore, pheromones can be categorized by their effects on the recipient animal, either as releaser or as primer pheromonal cues (Liberles, 2014; Tirindelli et al., 2009; Wyatt, 2014). Releaser pheromones induce immediate stereotypical behavioural responses, for example MUP-ligands that promote male–male territorial aggression (Chamero et al.,

2007), whereas primer pheromones induce delayed responses that are commonly mediated through activation of the neuroendocrine system, for example pregnancy failure upon detection of MHC class I of a stranger male (Bruce effect; Leinders-Zufall et al., 2004). In some cases the same pheromonal ligand can serve as either a releaser or a primer cue, or as both, depending on the recipient animal. For example, dehydro-*exo*-brevicomin (brevicomin) and 2-(*sec*-butyl)-4,5-dihydrothiazole (thiazole) are volatile testosterone-dependent pheromones that are found in male urine and act as releaser pheromones initiating male–male aggressive responses (Novotny, 2003). When detected by females, however, the same pheromones exert primer effects such as acceleration of puberty onset and induction of oestrus (Whitten effect; Jemiolo, Harvey, & Novotny, 1986; Novotny, Ma, Wiesler, & Zidek, 1999; Table 1).

## THE INTRINSIC REWARD VALUE OF PHEROMONAL STIMULI

The intrinsic reward value of an external stimulus can be inferred from the animal's first response to it. An approach response is an indication that the stimulus possesses positive value, whereas withdrawal or avoidance indicates a negative value (White, 2011). Releaser pheromonal signals that elicit approach behaviour often promote reproductive behaviours such as mating and aggression, and thus possess positive reward value. In contrast, pheromones with negative reward value typically elicit withdrawal or avoidance behaviours that may repress reproductive responses. Hence, the reward value of pheromones may govern the animal's behavioural decision to enter either a reproductive state or a state such as defence/avoidance. It has been suggested that these two states interact with and regulate each other (D. J. Anderson, 2012; Tinbergen, 1969). It should be noted that in some cases, the reward value of a pheromone may be a direct consequence of the behavioural action it triggers, and that when presented apart from the behavioural context it will have no reward significance. For example, it has been demonstrated that it is only subsequent to sexual experience that sexual pheromones elicit activation of the brain's reward areas in the opposite sex (Hosokawa & Chiba, 2005, 2007; Swaney, Curley, Champagne, & Keverne, 2007).

Pheromones that naturally possess positive value and elicit approach and attraction include, for example, the chemical agent dodecyl propionate. This pheromone is secreted from the preputial glands of rat pups, is detected by the dam's VNO and induces approach and maternal anogenital licking, which are essential for the pup's survival (Brouette-Lahlou et al., 1999; Mucignat-Caretta, Redaelli, & Caretta, 2012; Schaal, 2010). Furthermore, lactating female rats release chemosignals that attract their juvenile offspring (Leon & Moltz, 1971; Vaglio, 2010). Additional examples of pheromones with expected positive value are sexual pheromones. Female mice are attracted to specific volatile chemosignals found in male urine, such as thiazole, brevicomin (Garratt, Stockley, Armstrong, Beynon, & Hurst, 2011; Jemiolo, Alberts, Sochinski-Wiggins, Harvey, & Novotny, 1985) and  $\alpha$ - and  $\beta$ -farnesenes (Jemiolo, Xie, & Novotny, 1991; Zhang, Sun, & Zhang, 2010). Major urinary proteins (MUPs), which are abundantly secreted in the urine of male mice and serve as sex-specific pheromonal signals, possess innately rewarding values (Chamero et al., 2007; Papes, Logan, & Stowers, 2010; Roberts et al., 2010). For example, the MUP darcin (MUP20), a nonvolatile sex pheromone protein highly abundant in male mouse urine, binds the volatile male pheromone thiazole (Roberts et al., 2010). When presented on its own it was found to innately attract females. Furthermore, when darcin was added to the urine of BALB/c male mice, which normally express very low darcin concentrations, it rendered the previously unattractive urine appealing to females (Roberts et al., 2010). MUP-ligand complexes also have positive reward effects on male mice as they trigger approach behaviour and promote male–male territorial aggression (Chamero et al., 2007).

Pheromones that discourage social interaction and may elicit avoidance behaviour (or inhibit attraction), and thus presumably possess intrinsic negative value, are alarm pheromones that are emitted by stressed conspecific animals and signal injury, distress or predator presence (Weldon, 1983). In rodents, detection of alarm pheromones released from a stressed conspecific animal heightens stress response behaviours (Brechtbuhl et al., 2008; Kikusui, Takigami, Takeuchi, & Mori, 2001), increases plasma corticosterone levels (Brechtbuhl et al., 2013) and may inhibit sexual behaviours in males (Kobayashi, Kiyokawa, Takeuchi, & Mori, 2011). Another pheromone possessing a powerful inhibitory effect is the exocrine gland-secreting peptide 22, a nonvolatile ligand secreted from the lacrimal gland and released into tears of juvenile mice.

This protein exerts an inhibitory effect on consummatory sexual behavioural responses of receiver adult males (Ferrero et al., 2013).

The chemical cues that carry the most obvious negative intrinsic value for all mammalian species are predator-specific odorants (kairomones). In mice, predator olfactory signals such as 2,3,5-trimethyl-3-thiazoline and cat odours are detected by the MOE and the VNO systems of the receivers and elicit robust innate avoidance behaviours (Knaden & Hansson, 2014; Staples, McGregor, Apfelbach, & Hunt, 2008; Table 1).

Despite the fact that pheromones in most cases possess an intrinsic reward value and trigger or repress various innate reproductive behavioural responses, past learning experiences may induce dramatic changes in pheromone-mediated innate behaviours. For example, after undergoing sexual interaction with female conspecifics, sexually experienced male rats exhibit stronger preference than naïve males for female urine (Brown, 1977; Lydell & Doty, 1972). The production of female urine-elicited ultrasonic vocalizations in adult male mice was also found to be greatly dependent on previous experience. Male mice that were allowed to investigate a female for several minutes displayed higher ultrasonic vocalization responses than male mice not previously exposed to female urine (Dizinno, Whitney, & Nyby, 1978; Nyby, Wysocki, Whitney, Dizinno, & Schneider, 1979).

## PHEROMONE-MEDIATED CONDITIONAL ASSOCIATIVE LEARNING

In addition to the role of pheromonal stimuli in mediating unconditioned innate behaviour, accumulating evidence supports their role in reward-associated conditional learning (Brennan & Keverne, 1997; Kobayakawa et al., 2007; Tirindelli et al., 2009). One such type of pheromone-mediated learning can occur by association through classical (Pavlovian) conditioning (Pavlov, 1927). Classical conditioning occurs when an association is formed between two stimuli: a neutral conditioned stimulus (CS), which does not elicit a specific response, is paired with an unconditioned stimulus (UCS) that induces a specific unconditioned response (UCR). After the association is formed, the CS by itself will elicit a conditioned response (CR) that is identical or similar to the UCR (Pfaus et al., 2001; Rescorla, 1988).

Since pheromones elicit unconditioned innate responses, they can be used as unconditioned stimuli in classic conditioning paradigms. For example, the urine-borne volatile scent of a male mouse (CS), which initially is not attractive to sexually naïve females, becomes attractive and acquires positive reward value following its association with nonvolatile pheromones (UCS) that have intrinsic positive value and trigger innate appetitive behaviour (Moncho-Bogani, Lanuza, Hernandez, Novejarque, & Martinez-Garcia, 2002). The adaptive value of such associative learning is that the female will now also be able to locate an appropriate mating partner by using airborne chemicals that can be detected from a distance (Hurst, 2009). Moreover, female pheromones can be associated with neutral cues so that the latter will elicit reproductive-related endocrinological changes in males, such as increases in luteinizing hormone and testosterone secretion, which normally occur following exposure to females (Graham & Desjardins, 1980; Pfaus et al., 2012).

Pheromones are also crucial for pup suckling behaviours. In the European rabbit, *Oryctolagus cuniculus*, a chemical in its milk (the mammary pheromone; see Table 1) elicits innate attraction and suckling behaviour in newborn rabbit pups upon their first contact with the nursing female (Schaal et al., 2003). The mammary pheromone is sufficient to induce classical associative learning, as pups can acquire a conditioned response to a new odorant (CS) 1 day after the latter is paired with the mammary pheromone used



as the US (Coureaud et al., 2006). This appetitive learning functions efficiently enough to elicit nipple search behaviour in a single and brief pairing between the CS and the US. In contrast, it has been recently shown in mice that the first suckling does not reflect a pheromone-mediated innate response, but rather involves a learning process in which the neonate needs to have had previous experience with the maternal olfactory stimuli (amniotic fluid signature mixtures of unidentified volatile odorants; Logan et al., 2012).

Pheromones have also been shown to be sufficient to induce conditional place preference (CPP) learning. For example, the sex pheromone darcin can induce a learned attraction to the volatile urinary odour of the producer (Roberts et al., 2010) and can therefore be used as a reinforcer in spatial learning tasks (Roberts et al., 2012). In the latter study it was shown that darcin alone can promote spatial learning in mice, as both female and male mice remember the location that was previously associated with darcin and develop a CPP for this location (Roberts et al., 2012). Similarly, adult male hamsters, *Mesocricetus auratus*, can form a CPP to pheromone-containing vaginal secretions, indicating that these pheromone signals are innately rewarding for these animals (Bell, De Lorme, Figueira, Kashy, & Sisk, 2013).

In light of these studies, it is reasonable to ask whether the 'reinforcement strength' of reproductive pheromones differs from that of other biologically important natural stimuli. Interestingly, in hamsters it has been shown that vaginal secretions are as efficient as food or odour rewards in training the animals to press the bar in operant conditioning tests (Coppola & O'Connell, 1988).

#### LEARNING CAN OVERRIDE INTRINSIC REWARD VALUE

In general, the rewarding properties of odour stimuli that are either appetitive or aversive can easily be modified and their value can even be reversed by associative learning experiences. The unconditioned aversive odour of cadaverine, for example, can become less aversive and even attractive to rats following its association with sexual rewards (Pfaus et al., 2012). Peppermint odour, which is aversive to rat pups, can become attractive following its association with tactile stimulation that mimics the rewarding action of suckling (Yuan, Harley, & McLean, 2013).

This raises the question of whether the reward value of reproductive pheromones that possess innate biological messages can be as easily modified through associative learning. If so, to what extent are the intrinsic rewarding properties of reproductive pheromones mediated by past experience? In other words, will it be as easy to devalue the intrinsic value of reproductive pheromones as to devalue that of other natural rewarding stimuli?

Studies in rodents have shown that pheromonal signalling can acquire different appetitive or aversive values and mediate different behavioural responses as a consequence of either instrumental or classical conditioning. In instrumental learning paradigms (also known as operant conditioning), behaviour undergoes a change in frequency as a result of contingent reinforcement or punishment (Skinner, 1969). For example, when repeated presentations of female urine are not followed by the female itself (contingent punishment), male mice stop producing ultrasonic vocalizations in response to the urine (Nyby, Whitney, Schmitz, & Dizinno, 1978). In addition, the power of pheromones to induce male mice to initiate aggressive behaviour towards intruder males is weakened following defeat. The repression of appetitive behaviour and induction of avoidance behaviour have been suggested to be the result of a change in the reward value for the male, owing to an association between the rival's urine and the unfavourable (negative) outcome (Jones & Nowell, 1973; Potegal, 1979).

Furthermore, in classical conditioning learning, by associating pheromones with an unconditioned stimulus that possesses a reinforcing value opposite to theirs, animals may transfer the new (opposite) value to the pheromonal cue itself. In male rodents, pairing of a female pheromone source (e.g. urine or vaginal secretion) with a visceral malaise induced by lithium chloride injection resulted in a decrease in the reward value of the female pheromonal signal. This pheromone-mediated aversive learning led to a decrease in sexual appetitive behavioural responses such as approaching and licking/sniffing of the vaginal secretions (Johnston & Zahorik, 1975; Kay & Nyby, 1992; Zahorik & Johnston, 1976) and repression of copulatory behaviour (Peters, 1983).

The findings described above indicate that the presumably hardwired, closed behavioural program triggered in response to pheromonal cues in mammals is in fact a largely flexible system that can be altered as a result of pheromone-associative learning, thereby acquiring values that are different from and even opposite to the expected intrinsic reward values. Interestingly, it seems that pheromone-mediated appetitive behaviours (such as approach and sniffing behaviour) are more easily modified than consummatory aspects of pheromone-induced sexual behaviour (e.g. copulatory behaviour; Ball & Balthazart, 2008; Peters, 1983; Zahorik & Johnston, 1976).

#### PHEROMONE-MEDIATED LEARNING IN INSECTS

Learning in insects has received relatively little research attention probably on the assumption that insect behaviour is guided mainly by instincts (Dukas, 2008). However, it is becoming widely accepted that learning processes play a crucial role in behavioural decisions made by insects (Leadbeater & Chittka, 2007). More specifically, it is evident that the innate behaviours of insects, as of mammals, are flexible and prone to change as a result of previous learning experiences. For example, through associative learning, bees, *Apis mellifera*, can learn that the Nasonov pheromone, which innately attracts bees to food and water resources, is associated with the occurrence of a foot shock, and accordingly they modify their response towards it from approach to an aversive conditioning that elicits the sting extension response (Roussel, Padie, & Giurfa, 2012). Associative olfactory learning has also been shown in mosquitos, *Aedes aegypti* (Menda et al., 2013) and fruit flies, *Drosophila melanogaster* (Wright, 2014).

In *Drosophila*, male courtship behaviour is modified by prior sexual experience. To reduce competition from other males, the *Drosophila* male transfers to the female, during mating, a volatile aversive pheromone, *cis*-vaccenyl acetate. When a new male attempts to mate with a mature mated female, this compound becomes associated with female pheromones and leads to a general suppression of courtship behaviour towards all females (Ejima et al., 2007). Moreover, after a failure to copulate with a virgin female, males avoid courting with all females of the same age, since they associate the failure to mate with the chemical cues specific to the age of the female (Ejima, Smith, Lucas, Levine, & Griffith, 2005). In these examples, the innate sexual implication of female pheromones is altered to convey a different meaning and to reduce courtship and mating behaviour.

Male moths, *Spodoptera littoralis*, innately have marked sensitivity to the sex pheromone of the females (Greenfield, 1981). Past experience with sex pheromones of the female moth increases the sensitivity of the male's central nervous system to the female pheromone, which coincides with increased behavioural attraction to it (Anderson et al., 2007).

Thus, learning and neuronal plasticity in preprogrammed pheromone-mediated reproductive responses is not a prerogative of mammals. Insect pheromones can similarly participate in

learning, and can be conditioned to manifest an appropriate behavioural response.

### NEURAL REPRESENTATIONS OF OLFACTORY-MEDIATED REPRODUCTIVE RESPONSES

In rodents, increasing evidence indicates that chemical signals sensed via the MOE and the VNO function synergistically in the regulation of innate reproductive responses (Keller, Baum, Brock, Brennan, & Bakker, 2009). Studies in mice in which odour-triggered signalling by the MOE or VNO has been genetically disabled showed that the normal display of reproductive behaviours requires the coordinated function of both of these olfactory epithelial systems. Genetic silencing of VNO or MOE signalling is accomplished via knockout of genes encoding the ion channels of either the TrpC2 (transient receptor potential channel) or the OCN1 (olfactory specific cyclic nucleotide-gated channel), respectively. TrpC2<sup>-/-</sup> mutant male mice appear perfectly capable of reproducing, showing no reduction in courtship and mating behaviour towards females. These mutant males, however, display loss of sexual behavioural preference for females and increased mounting behaviour towards alien males (Leypold et al., 2002; Stowers, Holy, Meister, Dulac, & Koentges, 2002). Similarly, TrpC2<sup>-/-</sup> mutant females display loss of sexual preference, deficits in sexual approach/olfactory investigations and male-typical mounting behaviour towards both sexes (Chalfin et al., 2014; Kimchi, Xu, & Dulac, 2007). Furthermore, surgical ablation of the VNO system in sexually naïve females eliminates their preference for nonvolatile pheromones derived from gonad-intact rather than castrated males, as well as their preference for intact males rather than females. This further suggests that sexual olfactory preference and the motivation to approach and investigate potential mating partners are largely mediated by the VNO system when direct physical contact with nonvolatile pheromones is allowed (Keller, Pierman, Douhard, Baum, & Bakker, 2006). Further study is needed to determine whether the loss of VNO-mediated pheromone detection indeed affects the intrinsic pheromone-mediated or the learned reward value of pheromones, and in turn affects the motivation to approach and engage in appetitive reproductive behaviours (e.g. olfactory investigation, sniffing/licking behaviour). In a study with OCN1<sup>-/-</sup> mutant male mice, in which detection of MOE-mediated signals was blocked, olfactory cues were found to be essential for triggering the sexual approach and mating behaviours in mice as well as the initiation of aggressive behaviour (Mandiyan, Coats, & Shah, 2005). Moreover, removal of the VNO system in female mice did not impair their sexual preference for volatile odours, emphasizing the involvement of the MOE in addition to the VNO system in mate preference (Keller et al., 2006).

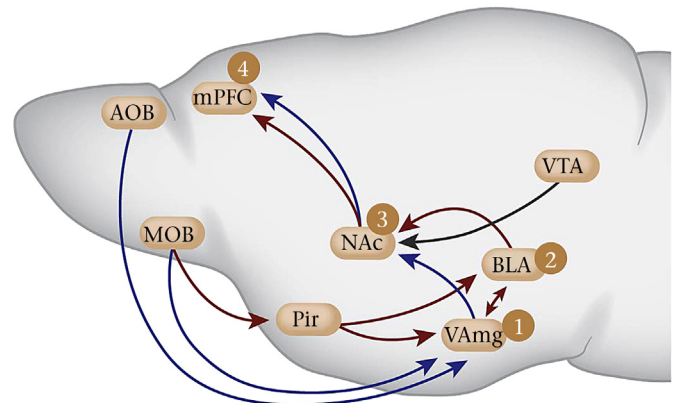
Furthermore, transfer of information between the MOE and the VMO systems has been found to be essential for establishing pheromone-associative learning (Keller et al., 2009; Martínez-García et al., 2009). As an example, the preference for male-derived volatile odours displayed by a sexually experienced female is a result of Pavlovian-like associative learning. The innately attractive VNO-detected nonvolatile pheromones were paired with MOE-detected neutral volatile molecules, such that the neutral odours were now tagged with positive emotional reward value and could elicit sexual olfactory preference on their own (Moncho-Bogani et al., 2002; Moncho-Bogani, Martínez-García, Novejarque, & Lanuza, 2005). In mice, blocking of both chemosensory systems is required in order to inhibit the acquisition of conditional place preference for oestrous female chemosignals in sexually naïve males (Korzan, Freatat, Johnson, Cherry, & Baum, 2013).

Hence, it seems likely that the intrinsic emotional value of pheromonal stimuli should be processed in brain centres where

inputs from the main and accessory olfactory systems converge, and then be relayed to the emotion-processing circuitry (Moncho-Bogani et al., 2002). Data on pheromone-induced neuronal activity obtained by detection of Fos expression in the brain strongly suggest that vomeronasal–olfactory associative learning takes place mainly in the basomedial and basolateral amygdala (BLA; Moncho-Bogani et al., 2005), where other forms of emotional learning, such as fear conditioning (LeDoux, 2000), also occur.

### OLFACTORY PROCESSING AND REWARD SYSTEMS

In rodents, the main olfactory bulb (MOB) projects directly to the olfactory/piriform cortex (Pir), olfactory tubercle, anterior and posterolateral parts of the cortical amygdala, anterior olfactory nucleus and lateral amygdala (Fig. 1). In contrast, direct projections of the accessory olfactory bulb (AOB) mainly target limbic brain regions including the bed nucleus of the stria terminalis, the accessory olfactory tract and the vomeronasal amygdala nuclei (VAmg) comprising the medial amygdala and posteromedial cortical amygdala (Fig. 1). The AOB projections also indirectly target hypothalamic brain nuclei, such as the medial preoptic area and ventromedial hypothalamus (Cádiz-Moretti, Martínez-García, & Lanuza, 2013; Dulac & Torello, 2003; Dulac & Wagner, 2006; Swanson, 2000). Interestingly, recent neuroanatomical tracing data demonstrate an extensive convergence of projections from the main and accessory olfactory brain regions in several cortical and noncortical amygdaloid structures including the medial amygdala, the anterior cortical nucleus, the cortex–amygdala transition area, the anterior amygdaloid area (Cádiz-Moretti et al., 2013; Gutiérrez-Castellanos, Pardo-Bellver, Martínez-García, & Lanuza, 2014; Kang, Baum, & Cherry, 2009; Pro-Sistiaga et al., 2007) and the posteromedial cortical nucleus of the amygdala (Gutiérrez-Castellanos et al., 2014) (Fig. 1). It is important to note that in a recent study it was found that MOE stimulation elicited hardly any response in the medial amygdala, and that the major input into the medial amygdala comes from the AOB (Bergan et al., 2014). Furthermore,



**Figure 1.** Neural encoding of the reward values of reproductive pheromones. Pheromonal signals are detected in the periphery by olfactory epithelia and transmitted to the main and accessory olfactory bulbs (MOB and AOB, respectively). 1. Pheromones with innate rewarding properties are further processed (blue arrows) in the vomeronasal amygdala (VAmg), which includes the medial and posteromedial cortical amygdala. 2. Pheromonal cues that do not possess intrinsic reward value (red arrows) are processed, via the piriform cortex (Pir) in the basolateral amygdala (BLA), where emotional tagging of previously neutral pheromones occurs. 3. Upon classification of the stimulus the amygdala influences the nucleus accumbens (NAc) via modulation of the dopaminergic neurons in the ventral tegmental area (VTA), resulting in encoding of the pheromonal reward value. 4. The medial prefrontal cortex (mPFC), on receiving projections from the NAc, executes goal-directed behaviour. Upon detection of conditioned odours, the mesolimbic dopaminergic pathway, which originates in the VTA and projects to the NAc, is activated (black arrow).

parts of the cortical amygdala of mammals display substantial projections to the BLA complex, which are considered as associative nuclei. Given that the cortical amygdaloid nuclei receive olfactory and vomeronasal projections from the olfactory bulbs, it is likely that the amygdalostriatal projections originating in these nuclei convey chemosensory information.

Manifestation of goal-directed behaviour relies on several neuronal networks incorporating the medial prefrontal cortex (mPFC), the nucleus accumbens (NAc), and limbic regions such as the amygdala and hippocampus (Mannella et al., 2013). Both the vomeronasal amygdala and the BLA extensively innervate the ventral striatum, which includes the core and shell of the NAc (Fig. 1; Korzan et al., 2013; Novejarque, Gutierrez-Castellanos, Lanuza, & Martinez-Garcia, 2011). It was demonstrated that rats trained to lever-press for a receptive female can subsequently be trained to lever-press for a light or a tone that is paired with copulation as a secondary reinforcement (Everitt et al., 1987). Lesions of the BLA selectively disrupted conditioned lever pressing for secondary reinforcement (Everitt, Cador, & Robbins, 1989), further supporting the idea that projections from the BLA to the NAc are required for the control of operant responding for sexual incentives (Fig. 1).

### INTERACTION OF DOPAMINE AND SEXUAL PHEROMONES

The mesolimbic dopamine pathway, which originates from the ventral tegmental area (VTA) and projects to striatal regions such as the NAc, has been implicated in the processing of both natural and drug rewards (Wise, 2004). A study in rodents showed an increase in dopamine (DA) concentrations in the NAc of sexually naïve male mice following their exposure to female urine (Malkesman et al., 2010). Moreover, naïve male rats exhibit transient DA elevations in the NAc when receptive females are presented, approached and investigated, all of which comprise the appetitive aspect of sexual behaviour (Robinson, Heien, & Wightman, 2002; Robinson et al., 2001). It is not yet known, however, whether pheromonal cues by themselves are rewarding and are sufficient to cause such elevations in DA or, as stated above, whether their rewarding properties derive from the rewarding act that they trigger, as in some studies no increase in DA is found when naïve males are exposed to female odours alone (Damsma, Pfaus, Wenkstern, Phillips, & Fibiger, 1992; Hosokawa & Chiba, 2005). In addition, studies on female mice demonstrated that their preference for investigating male soiled-bedding (containing pheromones) remains intact following lesions of VTA dopaminergic cells (Martinez-Hernandez, Lanuza, & Martinez-Garcia, 2006), after depletion of most of the dopaminergic fibres in the NAc shell (Martinez-Hernandez, Lanuza, & Martinez-Garcia, 2012), or after intraperitoneal administration of DA antagonists (Agustin-Pavon, Martinez-Ricos, Martinez-Garcia, & Lanuza, 2007). Although these studies do not indicate a lack of DA release in the NAc following the detection of sexual pheromones or the detection of chemosignals associated with the rewarding properties of sexual pheromones, they suggest that DA elevation in the NAc might not rely on a direct VTA–NAc pathway but rather on the projections to the NAc from the amygdala (Agustin-Pavon et al., 2007; Moncho-Bogani et al., 2005). This theory is supported by the finding that BLA inputs into NAc dopamine terminals synaptically facilitate the release of dopamine, independently of the firing rate of ascending VTA afferents (Floresco, Yang, Phillips, & Blaha, 1998; Jones et al., 2010; Fig. 1). Activation of the VTA–NAc pathway occurs in response to conditioned odours that receive their reward value through learning (Moncho-Bogani et al., 2005).

To summarize, we suggest that once olfactory and vomeronasal processing has occurred in the bulbs, representation of the biological meaning of the stimulus is further processed in the

amygdala where it undergoes neuronal classification (for example, classification of sex-specific pheromones that lead to distinct behavioural outcomes, occurs in the medial amygdala, Bergan et al., 2014). Upon classification of the chemosignal, the amygdala projects to the NAc to encode, possibly through dopamine release, the intrinsic motivational value of the stimulus (the vomeronasal amygdala–NAc pathway) or the acquired motivational value (the BLA–NAc pathway). The NAc then relays the information further to the mPFC, from where goal-directed behaviour is executed (Mannella et al., 2013; Fig. 1).

### SUMMARY AND DISCUSSION

In all animals, chemical cues are essential for locating potential food sources and detecting predators. Chemical cues, via detection of pheromones, also mediate conspecific social interactions and reproductive behaviours. In rodents, pheromone detection has been shown to play an essential role in triggering innate sexually dimorphic responses (Chamero et al., 2012; Liberles, 2014; Zufall & Leinders-Zufall, 2007). In male rats, for example, female pheromones usually lead immediately to initiation of fixed behavioural responses such as approach behaviour, olfactory investigation, ultrasonic vocalization and copulatory behaviour. In contrast, detection of male pheromones by males can promote approach or avoidance behaviour (depending on the social status), male–male aggression and territorial scent marking. In female rodents, male pheromones can induce approach behaviour, sexual receptivity (lordosis behaviour) and maternal aggression (Dulac & Kimchi, 2007).

It is commonly accepted that pheromonal stimuli possess unconditional intrinsic incentive value that is inherited, genetically programmed and triggered by hardwired systems. These stimuli are often qualitatively categorized as pheromones that carry attractive (positive reward) properties and induce a search for a mating partner as well as sexual behaviour and territorial behaviour, or as pheromones with aversive (negative reward) properties arousing avoidance/anxiety and repression of reproduction-related behaviours.

Hence, the attribution of an intrinsic reward value to pheromonal stimuli should allow the animal to accurately and efficiently elicit rapid behavioural responses without the requirement of a prolonged learning process. Such triggering of robust innate social and reproductive behaviours upon first exposure is clearly beneficial for the animal, prevents waste of time and energy and decreases the risk of predation. If the reward value of reproductive pheromonal stimuli and the behaviours they trigger are indeed purely genetically preprogrammed and controlled by hardwired circuits, it would be reasonable to assume that they would be restricted or precluded from flexible changes through learning processes.

In this review we have focused on the question of the extent to which innate reproductive responses mediated by pheromones are resistant to modifications through learning or, in other words, lack adaptive flexibility. A related question pertains to the degree, if any, to which the reward value of pheromonal stimuli can be altered or overridden by experience and associative learning to convey an updated biological message and mediate a better behavioural response.

We have presented various lines of evidence demonstrating that the expected intrinsic reward value of social and sexual pheromones mediating innate behaviours is flexible and can be altered through deliberate experimental manipulations by means of a simple reward-dependent (positive or negative) learning experience. Furthermore, through associative learning, pheromone stimuli can acquire a conditional reward value that may be



significantly different from and even opposite to their expected intrinsic emotional value.

Lorenz and Tinbergen defined innate behaviour as action that is hereditarily determined, is part of the animal's original constitution, arises independently of the animal's experience and environment, and is distinct from acquired or learned behaviour (Lehrman, 1953). According to this definition, many of the pheromone-mediated social and reproductive responses that are referred to here as innate behaviours appear to violate the criteria of innateness, and might instead be considered as learned behaviours having some species-specific innate characteristics. Hence, the classical use of the term 'pheromones' as signals triggering innate behaviour as opposed to signals (such as odours) that mediate learned behaviours might in many cases, as recently suggested by Doty (2010), be scientifically inaccurate. We argue that the intrinsic appetitive and aversive reward values of pheromonal stimuli underlying goal-directed behaviours are critically dependent, throughout life and in both sexes, on past experience and on conditional associative learning and memory. Hence, the innate responsiveness of an animal might be employed not to develop predetermined fixed behaviours but rather as an innate template for learning processes that determine the reward values of specific pheromonal stimuli.

Notably, the examples we provide in this review indicating plasticity in the values of reproductive pheromones are all derived from experiments carried out under laboratory conditions. Our current knowledge about how widespread such modifications are under natural conditions is seriously limited. Nevertheless, it is reasonable to assume that such flexibility is crucial for the survival and reproductive fitness of the organism, allowing rapid adjustments to constantly changing environments, for example when the environment lacks predators and there is a need to prevent overpopulation because resources are limited (Merton, Morris, & Atkinson, 1984) or when a threatening stimulus appears in the environment (Choi et al., 2005).

Lastly, the development of genetically modified mouse models in which signalling by odorants or pheromones or both is disrupted, combined with the availability of tools for measuring and manipulating neuronal activity and dopamine release within specific brain regions in animals performing particular behaviours, may improve the functional mapping of neural circuits underlying the emotional value of olfactory-induced reproductive responses.

## Acknowledgments

We thank Y. Ben-Shaul, the referees and the lab members for their useful comments and suggestions. This work is partly supported by the Peter and Patricia Gruber Research Award, the Women's Health Research Center of the Weizmann Institute of Science and the Joan and Jonathan Birnbach Family Laboratory Fund (T.K.).

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