Perception and emotions: On the relationships between stress and olfaction

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Abstract

Adaptations to the ever changing social and physical environment are necessary, sometimes involving the stress response. Olfaction is a chemical sense allowing the detection of molecules in the air and many species rely on it for social recognition and fundamental functions as feeding or reproduction. This non exhaustive literature review addresses three topics at the intersection of sensory biology and stress biology, in order to raise awareness and enlighten our understanding of animal behaviour. First we show that stress and associated emotions, such as fear can alter odour perception, from the sensor (peripheral nervous system) to the interpretation of the sensory input (brain). This can be of relevance for understanding the behavioural consequences of negative experiences and depression-like states. Second, odours involved in animal chemical communication can signal danger in the form of predators or stressed conspecifics, and in turn induce stress in recipient animals, as a form of chemical empathy. Finally, we review some of the evidence for the use of odours as stress-relief agents. There is no clear evidence of treatment efficacy and it might be that under the labels of inhalation aromatherapy, aromachology or pheromone therapy, a lack of perspective has led to the conflation of various biological phenomena: an alleged spontaneous olfactory effect on stress relief, environmental enrichment or the recall of positive emotional states. Careful experimental design and critical analysis are paramount to clearly evaluate this promising intervention. The world around us shapes our emotions, which in turn affect our perception. There might be a huge animal welfare potential to harvest from improved knowledge in the studies of stress and olfaction interactions, this will eventually allow us to show more empathy to animals in our care.

Keywords: stress; welfare; olfaction; odours

1. Introduction

We live in a world populated with more competitors and predators than friends, some of those interactions change over time and adaptation is often necessary. Sometimes, this requires action of the stress axis. Sensory information can guide and help animals adapt to their environment, in order to make sense of the ever changing world they live in. Food, sexual partners, friends or foes and the way home can be identified using various sensory modalities. Here, I will discuss examples of the reciprocal relationships between the olfactory perception of the environment and some of the emotions experienced by animals (in the wild or those managed by humans). This literature review addresses three topics at the intersection of sensory biology and stress biology, where an improved awareness can enlighten our understanding of animal behaviour and empower our efforts to improve animal welfare. There is a wealth of information on the topics addressed in this paper and for further general reading on olfaction biology please refer to specialised reviews (Apfelbach et al., 2005; Ihara et al., 2013; Li and Liberles, 2015; Nielsen et al., 2015a; Meunier and Rampin, 2017). The purpose here is not to exhaustively synthesise all the existing literature, but rather to give an overview of areas relevant to applied ethologists as a first step for people who might wish to work in this field, to widen perspectives and stimulate critical conversations and debates.

Humans can smell too!

First of all, in order to improve the reader's empathy towards the subject at hand, and emphasise how accessible the world of odours can be, let us discuss the capacity of detecting odours in *Homo sapiens*. Humans are allegedly microsmatic (low olfactory capabilities), whereas a large number of animal species are traditionally considered to be macrosmatic, they rely on odours and have higher sensory abilities. This notion may be based on culture rather than scientific observation, possibly based on hypotheses from the 19th century neuroanatomist Paul Broca (McGann, 2017) and stemming from a time when animals and humans were seen as fundamentally different. However, human microsmia has now fallen out of favour, with recent work highlighting sometimes comparable sensitivity between humans and other animals (McGann, 2017). The implication is that, although there is a degree of individual variability in our ability to perceive odours, experimental scientists and anyone involved in the keeping of animals should use their nose.

Perception and olfaction

Perception occurs when stimuli are detected and interpreted into a meaningful pattern. Odours are volatile molecules diluted in the air (or water), that are perceived by animals as olfactory sensation whose first step takes place through activation of sensory neurons. These are located in specialised tissues called neuroepithelia, at the interface between the environment and dedicated sensory structures in the brain. In most species this task is carried out by the main olfactory epithelium (OE, also known as olfactory mucosa), with contributions from the accessory olfactory system, composed of the vomeronasal organ (Mucignat-Caretta, 2010) or Grueneberg ganglia (Brechbuhl et al., 2008). The OE is generally considered to be involved in general odour recognition. The detection of odorant molecules consists in the translation of chemical signals into electric nervous message, this peripheral signal is then transmitted through the olfactory bulb to various brain structures that process emotion (e.g. amygdala) and learning (e.g. hippocampus). In comparison to other sensory modalities, the route of information is direct (Soudry et al., 2011). In contrast, audition and vision are connected to those emotional and cognitive structures via relays in specific thalamic nuclei and

subject to further processing and regulation (reviewed in (Wijesinghe et al., 2015). This closer neuroanatomical link between olfactory and limbic regions is deemed of great importance, when considering the impact odours can have on animal behaviour. Olfactory detection is a regulated process, it is likely to be altered by various endogenous signals, such as certain feeding-related hormones (Palouzier-Paulignan et al., 2012) and phases of the circadian cycle (Amir et al., 1999). The mechanisms through which the olfactory system and odour perception exhibit plasticity are diverse and some have been reviewed elsewhere (Wilson et al., 2004). Depending on the time scale and the nature of the event considered, they may involve rapid molecular events in response to leptin or insulin affecting olfactory neurone response in the OE (Palouzier-Paulignan et al., 2012), effects of signalling peptides on OE olfactory neuron cell survival or proliferation (Laziz et al., 2011), neural network rearrangement in cortical regions (reviewed in McGann 2015), and in the longer term, epigenetic alterations possibly affecting olfactory gene expression patterns have been identified in response to learning paradigms (Jones et al., 2008; Dias and Ressler, 2014). From the rapid effect of hormones within minutes, to the several days necessary for tissue level alterations, those factors contribute to modulate detection and response to all or specific odorant molecules. Individual variability in olfactory performance will therefore be the product of genetic factors (e.g. olfactory receptor polymorphisms), physiological factors (e.g. hormone levels and tissue sensitivity) and life history (previous exposure to odorants).

Odours can elicit various neuroendocrine processes that affect animal behaviour in an innate and/or learnt fashion, when an association between odours and other stimuli is created. Olfactory cues are important for the initiation and maintenance of feeding and reproductive behaviours, intra- or interspecific recognition of social cues and predators. The molecules that make up odours can be from environmental sources (e.g. food or plants) but can also originate from other animals and some of these have been identified as semiochemicals, i.e. chemicals of animal origin that affect the behaviour in a recipient. There are many types of semiochemicals, for instance pheromones are substances that affect behaviour in the same species and allelochemicals affect behaviour in other species. Further aspects of terminology and relevance to applied ethology have been discussed elsewhere (e.g. see reviews by Wyatt (Wyatt, 2014; 2017) or Nielsen (Nielsen et al., 2015b)). Like any sensory cues, odours can have different valence, they can be attractive or repulsive. This can vary due the ecology of the species concerned (predator odour generally elicits fear and avoidance in preys) and there are also individual preferences. Indeed, this can be altered by experience and learning (reviewed in (Nielsen et al., 2015b) and the same odorant can be attractive at low concentrations and aversive at high concentrations. For an accessible and more thorough primer on the mechanisms of olfaction, readers can refer to another review (e.g. (Meunier and Rampin, 2017).

Challenges of working with odours

For scientific investigators, olfaction is a field of sensory biology that can be technically challenging. The greatest difficulty lies with ensuring consistent stimulus delivery. Unlike other experimental treatments, such as dietary manipulation or drug injection, it is difficult to ensure the animal has smelled the test odour. The type of experimental paradigm used can affect the results, odour delivery can be affected by the size of the experimental arena in which the odours are presented, the distance to the odour source, and even the direction of the wind. Stressful experimental conditions (e.g. neophobia, strong lights or unusual sounds) can lead to the animal not investigating or inhaling the odorant source. Some researchers choose to ensure odorant exposure by diluting it in food or drinking water, at the risk of inadvertently studying the pharmacological or even toxicological effects of the chemical administered. Finally, depending on the type of animal testing facility used, physical

factors such as temperature, compound vapour pressure and air movement will affect odour volatility and spatial distribution. This can affect stimulus delivery or potentially lead to contaminations, such as when supposedly naïve animals might be exposed to test odour prior to the experiment. In addition, contaminating stimuli might originate from outside (e.g. grass cutting) or inside the facility (e.g. cleaning products adsorbed onto surfaces). Great care is therefore required when testing the relationship between animal behaviour and odours.

The stress response: a few reminders

Whether challenges result from environmental factors or other beings, the body constantly requires physiological adaptations to achieve homeostasis. Stressors are factors that constitute a real or perceived threat to the homeostatic drive of the individual and its survival. The stress response is the sum of psychic arousal and changes in affect associated with physiological reaction where resources are mobilised, to sustain metabolic and behavioural adaptations, and allow the classical 'fight or flight' reaction. It is induced by a vast range of psychological to physico-chemical factors. There is no Cartesian duality of mind and body here, mental and physical resources work together to survive a predator encounter or a chronic shortage of food.

This section is a brief reminder of stress biology notions and merely introduces some key players in the three stories to come (for a more extensive review, see (Goldstein, 2010)). Briefly, environmental stimuli that could threaten the animal modify the activity of various brain regions (e.g. hippocampus or amygdala) which in turn activate neurones in the posterior region of the hypothalamus, causing stimulation of the adrenal gland medulla via the splanchnic nerve, resulting in the rapid release of catecholamines, adrenaline and noradrenaline. Those fast acting mediators are responsible for the first signs of the stress response (increased cardiopulmonary function, sweating). In parallel, another part of the hypothalamus is also activated, the paraventricular nucleus (PVN). This leads to secretion of corticotropin-releasing hormone (CRH), that acts on the pituitary gland, which in turn sends messages through release of adrenocorticotropic hormone (ACTH), which travels via the bloodstream and in turn stimulates the cortex of the adrenal glands to release glucocorticoid hormones (predominantly cortisol in large mammals and fish; corticosterone in rodents and birds). Glucocorticoids affect metabolism, as well as a vast range of processes pertaining to immunity or brain function. Collectively those hormones are responsible for the adaptive effect of the stress response, this is called acute stress. If the animal is subjected to repeated and inappropriate stimulation of this stress response, pathologies can appear, this is called chronic stress (McEwen, 2007). The neuroendocrine response described above is accompanied by alterations in arousal and emotions. Mechanistically, the neuroendocrine and physiological changes concomitant with the stress response are causative of further behavioural effects, responsible for the fight of flight response(de Kloet et al., 2008).

The question of the effects of stress is still a matter of investigation, but several consequences have already been identified (some are reviewed in (Greenberg et al., 2002). A large number of behavioural effects have been identified and they are related to aggression and social interactions, sex, food intake, cognition and exploration (Greenberg et al., 2002). Behaviour changes in stressed animals are accompanied by increase in fear or anxiety, this is thought to prevent risk taking (Nettle and Bateson, 2012) and alterations in memory (de Kloet et al., 2008).

Over time, chronic stress can lead to the development of depressive-like symptoms (McEwen, 2007) with increased learned helplessness and loss of pleasure seeking (anhedonia, (Katz, 1982); inhibition of social behaviour (Beery and Kaufer, 2015); alterations in body grooming (Kalueff et al., 2016) and

increased aggressiveness (Neumann et al., 2010). Repeated exposure to stressors may have an impact on fearfulness, as shown in sheep exposed to six weeks of unpredictable stressors (Destrez et al., 2013). Overall, stress impacts affective states as well as emotions.

Emotions have previously been linked to perception, for pain, vision and gustation. In several animal models and human patients, associations have been reported between stress levels or mood disorders and sensory perception. In the case of pain perception, acute stress may have analgesic effects (Sorge et al., 2014), whereas chronic stress can cause hyperalgesia (Blackburn-Munro and Blackburn-Munro, 2001). Using electrical measurements of retina activity in response to visual stimuli, it was recently reported that depressed patients had lower retinal function, suggesting that vision can be affected by depressive disorders (Bubl et al., 2010). In human, subjects displaying traits of mild subclinical depression were asked to assess taste and fat content in test food, their ability to discriminate subtle variations was blunted compared to healthy controls (Platte et al., 2013). Overall, depressive-like mood and/or chronic stress appear to alter several aspects of sensory perception in animals.

2. The stress response impacts sensory perception

Olfaction is affected by acute stress

Here we argue that olfactory tissues are stress hormone responsive and function differently in people and animals with varying levels of stress, or when a negative association with an odour has been created (conditioning), and when suffering from stress-related mood alterations.

Hormones can be seen as the regulators of homeostatic coordination of physiology and behaviour, influencing a plethora of biological processes. In keeping with (and as an integral part of) this integrated control, olfaction has been shown to be affected by several hormonal factors. Depending on the state of satiety, food smells will not impact animal behaviour the same way, in part because the odorant signals are interpreted differently in the brain but also because they are detected differently; indeed, feeding-related hormones (e.g. insulin, NPY, leptin) affect olfactory function (Palouzier-Paulignan et al., 2012). Although less established, there is evidence for an olfactory regulation effect of stress-related glucocorticoid hormones (such as cortisol or corticosterone) whose secretion has profound impact on physiology and behaviour. Hormones act on receptors, and the presence of glucocorticoid receptors (GR) in a cell type or a tissue suggests the potential for responsiveness to this hormone. Peripheral nervous system and brain regions associated with olfactory response such as the olfactory epithelium, olfactory bulb and the lateral olfactory tract, express such receptors (Morimoto et al., 1996; Robinson et al., 1998). Receptors for other mediators of the stress response have also been identified in olfactory related regions: CRH (Garcia et al., 2016), ACTH (Mountjoy et al., 1994) and adrenaline (Kawai et al., 1999).

Given that several stress hormones originate from adrenal glands, interesting functional information can be gathered from situations when their function is altered. In patients suffering from adrenal insufficiency, with reduced cortisol production, olfactory perception threshold was reduced: these patients showed an increased olfactory sensitivity and this was reversed by steroid supplementation treatment (Henkin and Bartter, 1966). Some of the earlier studies in rat models provide conflicting evidence of adrenal hormone influence, following adrenalectomy olfactory performance was either

reduced (Sakellaris, 1972) or unaltered (Doty et al., 1991). Given that patients or animals with reduced adrenal gland function suffer from far more debilitating issues than altered olfaction, confounding factors are probably at play and clouding the issue.

More recently, research using subtler models has brought some elements of response to the question of how stress might impact olfaction. Some insights gained from human studies might inform us on homologous animal emotional states. In studies with healthy patients a link between cortisol level and olfactory function was investigated. In women, when olfactory detection threshold was measured across the menstrual cycle, increased cortisol was associated with improved odour detection abilities (Pause et al., 1996). In a postpartum study, higher cortisol levels were associated in new mothers with a greater attraction and a better ability to recognize their infants' odours (Fleming et al., 1997). Cortisol levels can be experimentally manipulated in human test subjects, for instance by inducing fear, such as in the Trier Social Stress Test where volunteers are tested following public speaking (TSST, (Kirschbaum et al., 1993)). In men subjected to a modified TSST, plasma cortisol levels were raised and the volunteers were found to experience more anger (Hoenen et al., 2017). Olfactory sensitivity was enhanced in those subjects. Interestingly, in physiologically stressed controls subjected to physical exercise and displaying similar signs of physical arousal, without the experience of fear, changes in olfactory function were not detected. This suggests that, in this paradigm, not all physiologically or metabolically stressful experiences lead to alterations in olfaction, it might have been the experiencing of emotions concomitant with the stress response that affected sensory perception. Although no attempts were made to accurately assess their emotional state, subjects submitted to a stressful mental arithmetic task in public, leading to stress-related increases in cardiopulmonary function and cortisol levels, performed better at detecting the rotten egg smell of 2-mercaptoethanol (Pacharra et al., 2016). A study in healthy patients showed that the emotional status affected olfactory function, high anxiety was significantly associated with reduced olfactory functioning for both odour detection and identification (Takahashi et al., 2015). In some cases, odour perception was not found to be affected, but the brain processes in response to odours presentation differed. A human brain imaging study (Krusemark et al., 2013) showed that the induction of a transient anxiety state in healthy patients altered activation response to odours in several brain regions and the functional interactions between those regions were also affected. In one of the few mechanistic studies of acute stress and olfaction in laboratory animal, adrenaline released during a mild stressor exposure was shown to act on the olfactory bulb to repress the formation of olfactory memories (Manella et al., 2013). Thus, a mildly stressed animal may not remember odours associated with the negative event in an odour recognition task. Altogether this supports the idea that behavioural responses to odours can be affected by stress and stress-related emotional states. Acute stress and the hormones associated herewith have been shown to affect several aspects of olfactory detection; overall it might be argued from available data that acute stress could enhance olfactory detection (Pause et al., 1996; Fleming et al., 1997; Pacharra et al., 2016; Hoenen et al., 2017). For practical reasons olfactory testing is primarily carried out with a limited number of odorant molecules. It is important to bear in mind that odours differ in their pleasantness or valence, and it is likely that stress affects the perception of different odours in different ways. This has not been studied, and an obvious experiment would be to test the effect of stress on the perception of aversive danger-related odours (predators), against more attractive odours with a positive valence (social partners, food).

Olfaction is affected by aversive learning

Exposure to aversive unconditioned stimuli may generate an initial stress response and associated emotions, such as fear, dependent on the degree of stimulus aversiveness. Associative learning may take place if exposure is repeated. When odorant conditioned stimuli are associated with aversive conditions, some studies show plasticity is induced in olfactory cells (Wilson et al., 2004; Jones et al., 2008; Tong et al., 2014), and the relatively longer lasting encoding of the negative association in tissue morphology (e.g. through DNA methylation marks, associated with change in numbers of specific olfactory sensitive neurones in the OE) leads to altered responses to odours. The time window for the creation of such association ranges from hours in the case of associative learning, to days or weeks, when cell and tissue morphological alterations are necessary. In fact, fear-based learning paradigms have been used to study the function and plasticity of the olfactory system. In a mouse model, electric foot shocks associated with acetophenone, an odorant molecule for which the olfactory receptor is known (M71), led to increased freezing in presence of acetophenone alone after 3 weeks of training, which is characteristic of Pavlovian conditioning (Jones et al., 2008). This learning was accompanied by increased number of neurons expressing the cognate receptor to this odorant, in the olfactory epithelium and olfactory bulb glomeruli. This morphological change is an example of experience-dependent plasticity in the olfactory system, induced by learning, which requires further validation in other models. Surprisingly, in this study, where the perception of a specific odorant was increased in negatively conditioned mice (after 3 weeks of associative learning with foot shocks), there was no indication that the mice were chronically stressed. Work from the same laboratory went on to show this phenomenon was reversible, as the memory extinction was accompanied by a loss of M71 overexpression (Morrison et al., 2015) and might possibly be epigenetically transmitted through the paternal germline (Dias and Ressler, 2014): in other words, the naive offspring of conditioned males displayed increased fear to acetophenone, through sperm-based transmission of information. Some of those spectacular claims will have to be verified through reproduction in other laboratories, as doubts about their validity have been cast due to an improbably high number of reported significant p-values (Francis, 2014). Other investigators have also described examples of plasticity in the mouse brain in response to fear-based learning. Following 3 days of the odour-foot shock paradigm, olfactory bulb nerve outputs in response to the threat-predictive stimulus (i.e. the odour) were altered, thereby facilitating learning of the aversive association (Kass et al., 2013). Using a similar experimental set up in human volunteers (finger electric shocks paired with odours), the hypothesis of aversive conditioning-mediated olfactory neuroplasticity was tested, and olfactory detection threshold was lowered following repeated conditioning events (Parma et al., 2015). Finally, using electro-olfactogram in human to study olfactory mucosa function, unpleasant electric shocks on the wrist administered in the presence of odours led to peripheral alterations in odour sensitivity (Cavazzana et al., 2018), thereby supporting some of the earlier findings in mice described above (Jones et al., 2008). The mechanisms at play are not known but interestingly, to further describe this phenomenology, it should be noted that appetitive (i.e. positive) conditioning might also affect olfactory neuron numbers (Jones et al., 2008). Mice for whom acetophenone was paired with cocaine exposure also had more M71 receptor expression, suggesting this plasticity might be at least partly relevant to stimulus salience and the arousal associated.

The fast and efficient detection of odours learnt to be associated with threats could provide a number of adaptive benefits (McGann, 2015). Associative learning is generally considered to affect cortical brain regions involved in memory and emotion processing (e.g. hippocampus). Recent work suggests that sensory systems might be subject to similar anatomical and functional plasticity, during the learning process. The behavioural consequences of those adaptations reflect the changes in olfactory sensitivity and signal processing. It would be interesting to test whether these mechanisms occur in species other than laboratory rodents and humans.

Olfaction is affected by chronic stress and associated emotions

Repeated exposure to stressful situations has been shown to affect emotions and perception of odours. This is especially in the case of unpredictable and heterospecific stressors, where little or no learning and habituation can occur, and when there is a perceived lack of control (Weiss, 1972). Chronic stress has global effects on metabolism and the immune system, which can shape and affect the substratum for animal behaviour (the brain) and any epithelium of the body (including the olfactory epithelium). Classically, chronic stress is known to affect brain structures involved in emotion processing and memory formation: the prefrontal cortex, the hippocampus and amygdala (fear associated region). Chronic stress induced alterations of those structures can lead to mood changes and promote the onset of anxio-depressive symptoms in human (Anacker et al., 2011); this can be used to induce anxious- and depressive-like symptoms in experimental animals.

Although not classical depression symptoms, a number of olfactory-related anomalies have been identified in depressive patients, from loss of sensitivity (Buron and Bulbena, 2013) to alterations in the pleasant sensation brought by odours (olfactory anhedonia, (Naudin et al., 2012)). A recent meta-analysis finds most published studies agree on this olfactory loss in depressive patients, but the heterogeneity in methods used to assess olfactory function hinders the identification of mechanisms (Taalman et al., 2017). In patients suffering from panic disorders, although odour perception was not reported to be affected, brain imaging studies showed that brain regions were differently activated in response to odours, suggesting alterations in the way the information is processed (Wintermann et al., 2013). Recent work has contributed to the understanding of those phenomena, using models where mood was experimentally altered through chronic stress exposure in laboratory rats. In our laboratory, we recently demonstrated that the first step of olfactory detection was functionally reduced, in the olfactory epithelium following a regimen of chronic variable stress (CVS, with unpredictable stressors), where rats developed depressive-like symptoms (Raynaud et al., 2015). This loss of function was concomitant with a decrease in olfactory neuron cells lost by apoptosis. This work was greatly extended by another team, using a similar model, where it was shown in several tests that CVS led to a reduction of olfactory driven behaviours and changes to a brain region involved in the transmission of olfactory information, the nucleus of the lateral olfactory tract (nLOT, (Vaz et al., 2018)). CVS rats suffered from a loss in olfactory sensitivity towards social or food odours, and exhibited deficiencies in behaviours induced by odours: for instance, there was a loss of attraction and loss of aversion to odours that are respectively innately attractive and repulsive to control rats. Interestingly, following a four-week recovery period, some of those deleterious effects persisted, suggesting chronic stress might have lasting effects on olfactory function. It should be noted that it is difficult to ascertain treatment effects on olfactory changes in depressed animals, since loss of response to odours could indicate a loss of olfactory perception, but also a loss of motivation and emotional reactivity, symptoms also encountered in those models. In addition to those CVS models, the links between olfaction and anxiety/depression have been explored in another model, where mice chronically treated with corticosterone in their drinking water developed anxious and depressive-like disorders (Siopi et al., 2016). Those alterations were accompanied by changes in cell survival in the olfactory bulb and a loss of olfactory discrimination, acuity and memory at the behavioural level. The induction of olfactory loss has also been reported to induce depressive symptoms. Olfactory bulbectomy, the surgical removal of rodent olfactory bulb, has been extensively used as a depression model (Kelly et al., 1997; Song and Leonard, 2005). Although its mechanisms of action are not fully understood, bulbectomy probably involves disruption of the cortico-hippocampal-amygdalar circuit (Song and Leonard, 2005). Also, in rodents (Glinka et al., 2012; Chen

et al., 2014) and fish (Abreu et al., 2016) animal models where olfactory sensitivity is reduced through genetic modification of the olfactory detection machinery, anxiety- and depressive-like effects can be detected. One can hypothesise that the sensory deprivation these animals experience might negatively impact their welfare and their mood.

Collectively these studies show that fear and negative experiences can alter odour perception, from the sensor (peripheral nervous system) to the interpretation of the sensory input (brain). Bearing in mind that the keeping and production of animals can lead to stress, the next obvious question is whether these laboratory observations are of relevance to other species and whether captive animal welfare could be improved by taking those findings into account.

3. Odours can induce a stress response

As described above, olfactory signals are potent conditioned stimuli in associative fear learning. In certain species, olfactory signals can also induce fear and stress reactions in an innate fashion. Those semiochemicals serve a wider purpose of communicating information about various aspects of physiology, such as reproductive status, food preference, or the presence of danger. Animals can infer much information from chemical cues emitted by others, and those contribute to many adaptive behavioural responses, depending on the ecological niche and living style of the animal. For a comparative review of those signals in species as different as mouse, insects and the worm *Caenorhabditis elegans*, see a review by Ihara (Ihara et al., 2013).

Odours as potential predation signal

Unusual or abnormal environmental signals can cause alarm and induce a stress response. A strong, unpleasant odour or the smell of something known to be dangerous (e.g. fire) will signal a potential danger and can be physiologically translated into a stress response. But the reason why the annual biology department BBQ is not usually a source of intense fear and acute stress is that other contextual cues allow for a more thorough and accurate assessment of the situation (odour of burgers and the sight of friendly colleagues).

Strong unpleasant smells can make us feel uncomfortable. For instance, they may signal rotten food, and we seek to avoid them. Butyric acid is the product of fatty acid degradation by bacteria and is well known for smelling like rancid butter or sweaty armpits. TMT (2,5-dihydro-2,4,5-trimethylthiazoline) is also known for its unpleasant scent, and has long been considered to be the main fear-inducing component of fox faeces odour, though this has recently been challenged (Rampin et al., 2018). It is nevertheless recognised for its fear-inducing properties in rodent preys. When rats were allowed to explore a test arena containing butyric acid or TMT in one corner, they avoided spending time near the odorant source (Endres and Fendt, 2009). However, unlike butyric acid, TMT also caused an increase in the amount of time the rats spent freezing. Freezing is a transient immobilisation whilst the rat appears alert, thought to help reducing harm in threatening situations and classically recognised as a fear-related behaviour. This finding therefore shows that it is not only unpleasantness that drives seemingly innate fear behaviours but that certain compounds specifically induce a fear reaction.

In addition to using fox faeces, scientist have induced fear in rodents using a variety of odours sourced from diverse predator species (felidae, canidae, bear): cloth rubbed on fur, used bedding, anal gland secretions, faeces and urine (Apfelbach et al., 2005). Preys sensitive to predator odour include wild and domesticated animals from a wide range of species: rodents (mouse, rat, vole), rabbit, hare, goat, deer, beaver, cattle and sheep.

Some fear inducing compounds have been purified in predator secretion, in addition to TMT, mostly various pyridine analogues (Brechbuhl et al., 2015) including 2-phenylethylamine (PEA;(Ferrero et al., 2011)). There is evidence that the fear-inducing properties of predator smell are dependent on their meat-based diet, leading to sulphur and nitrogen-rich faeces (Nolte et al., 1994; Berton et al., 1998; Apfelbach et al., 2015; Osada et al., 2015). Urine from coyotes fed melon did not cause the same avoidance reaction as urine from predators fed meat in four prey species: the mountain beaver (*Aplodontia rufa*), the house mouse (*Mus musculus*), the deer mouse (*Peromyscus maniculatus*), and the guinea pig (*Cavia porcellus*) (Nolte et al., 1994). Faeces collected from cats fed either a vegetarian diet or freshly killed mice: exposure to the faeces was tested in an exploratory task using mice, and the meat faeces caused a reduction in exploration and induced more anxious-like behaviours (Berton et al., 1998). The impact of predator scent on prey is also stronger when presented as a complex bouquet of several odours, rather than as single isolated molecular odorants (Apfelbach et al., 2015).

Animals sensitive to predator odours display a hormonal stress response, as evidenced by increases in blood pressure and plasma cortisol or corticosterone levels (e.g.(Takahashi, 2014). This stress response will in turn affect various biological function, including brain functions. Behavioural responses of prey to predator odours have been extensively reviewed elsewhere (Apfelbach et al., 2005); these responses include freezing, avoidance behaviour, defensive burying, reduced or delayed eating, and changes in the acoustic startle response (reaction to a sudden loud noise).

In rodents, and possibly other species, several structures are dedicated to odour recognition and are involved in fear-related molecule detection (Takahashi, 2014): the main olfactory epithelium, the vomeronasal organ or the Grueneberg ganglia (Brechbuhl et al., 2013; Brechbuhl et al., 2015). Different brain regions will also be activated by different fear-inducing odorants and this may translate into slightly different physiological and behavioural responses (Takahashi, 2014). The neural pathway of TMT-induced fear and stress responses has recently been described in detail (Kondoh et al., 2016). Upon odour detection, the olfactory bulb is directly connected to a brain nucleus related to the amydgala, the amygdalo-piriform transition area, which in turn activates the paraventricular nucleus of the hypothalamus and induces the endocrine stress response (corticosterone production). This neuroendocrine activation pathway is an interesting illustration of the intimate neuroanatomical links between olfactory and stress response pathways.

Responses to frightening predator odours vary between individuals. It is thought that antipredator behaviour is primed by genetic factors, and triggered by life experiences. These variations are the product of genetic variability (e.g. in emotional or endocrine responsiveness, or in different species) and life experience (e.g. previous stress exposure). In rat, strain differences have been shown in fear responses to TMT, for instance between Sprague-Dawley, Long-Evans and Wistar rats (all albino laboratory rats), the latter being less responsive in terms of freezing (Rosen et al., 2015). In response to fox faeces, Wistar rats and the pigmented Brown Norway strain differed in the duration and occurrence of freezing behaviour (Rampin et al., 2018). There are several reports that TMT or cat urine do not always induce freezing or avoidance in laboratory and field conditions (Apfelbach et al., 2005). A rarely discussed but plausible explanation could be that over the decades of experimentation with laboratory rats, which are bred captive in small plastic boxes and in the absence of foxes or cats, the innate fear of TMT trait disappeared because of the lack of selective

pressure to maintain it. A recent study supports this hypothesis, where after 13 generation of being geographically segregated on an island from their dingo predators (*Canis familiaris dingo*), Northern quolls (*Dasyurus hallucatus*) marsupials were tested for their response to predator odour (Jolly et al., 2018). In comparison to quolls born and raised in the vicinity of dingoes, island quolls exhibited no signs of fear or recognition in response to predator fur, even though they had cohabited for millennia prior to island segregation. Several studies point to the role of past experience. For instance in cows, the response to wolf urine odour (together with auditory stimulation of recorded wolf howling) was increased in animals bred in areas inhabited by wolves, in comparison to naïve animals who had not experienced wolves (Cooke et al., 2013). In other ungulates, the heart rate of elk (*Cervus elaphus canadensis*) exposed to various predator odours was highly variable between individuals (Chabot et al., 1996). The effect of life experience also applies to attempts to repel rodents using odour sources: they can become less effective, as there is evidence of habituation following repeated exposure to commercial prey repellent (Apfelbach et al., 2005). Olfactory driven behaviours can be altered in sick individuals. It has been reported that infection with the parasite *Toxoplasma gondii* can lead to alterations in olfactory perception of fear related odours. Infected rats might become less fearful of cat odours (Vyas et al., 2007), thereby leading to higher chances of an unfortunate final meeting with the predator and increased transmission of the parasite. This phenomenon is still a matter of debate (Worth et al., 2013).

Odours that signal stress to conspecifics

Many animal species express prosocial behaviours homologous to what is known as empathy in humans. For instance, the prairie vole (*Microtus ochrogaster*) provides support, in the form of grooming, to conspecifics that have suffered from adversity (Burkett et al., 2016). Farmed pigs have been reported to show signs of emotional contagion, both for positive and negative emotions (Reimert et al., 2013). Odorants, either as a single compound or as a mixture, can be used to transmit information about emotional states; these are sometimes referred to as 'alarm pheromones'. This olfactory-based empathy, a form of chemical communication through social signalling of arousal in animal groups, provides an evolutionary advantage, as it warns individuals to possible threats experienced by others. Although admittedly less efficient and slower than other visual or auditory signals, those odorant molecules are the volatile homologues of sonic alarm calls and one could hypothesise they are stealthier (if they do not spread too far), preventing the advertisement of one's presence to predators.

Some of those olfactory signals can be detected in faeces and urine. Naïve rats can distinguish between faeces from chronically or acutely stressed and non-stressed conspecifics (Valenta and Rigby, 1968; Mackay-Sim and Laing, 1980; Bombail et al., 2018a). In addition, rats can also distinguish faeces from stressed chickens (Bombail 2018), suggesting the potential for heterospecific recognition of distress. Urine also contains distress signals, transmitting negative experiences to naïve conspecifics, as has been demonstrated in species of agricultural interest. In pigs, when a food dispenser was sprayed with urine from a restrained animal, the latency to feed from it was longer than when sprayed with control urine, a sign of distress (Vieuille-Thomas and Signoret, 1992). In an experiment with cows, naïve individuals also exhibited a longer latency to feed in the presence of urine from a heifer subjected to electric shocks (Boissy et al., 1998). The smell of stressed heifer urine also induced a rise in cortisol levels in the exposed animals. Alarm pheromones are not limited to animal dejections: various stressors have been shown to cause the production of an airborne signal inducing a number of physiological and behavioural stress responses in naïve rats (Kiyokawa et al.,

2013). In anaesthetised rats, electric stimulation of the perianal gland lead to the production of this alarm pheromone (Kiyokawa et al., 2013; Inagaki et al., 2014).

As seen above, some of those odorant signals may originate from glands. Analytical chemistry has allowed the identification of some alarm substances. In the case of the rat alarm pheromone, a mixture of two compounds (4-methylpentanal and hexanal) is reported to be responsible for the stress information transfer (Inagaki et al., 2014). Stressed mice secrete a sulphur-containing volatile compound that shares chemical features with compounds from the urine of meat-eating predators (2-sec-butyl-4,5-dihydrothiazoles). Mice use it to signal non-specific dangers to others, as this alarm signal is detected by the Grueneberg ganglia (Brechbuhl et al., 2013). It has been hypothesised that some of these odorants have been evolutionarily borrowed from predator species, hence their categorisation as not only pheromones but also kairomones, a substance benefiting a receiver from another species (Brechbuhl et al., 2013). Additionally, adrenaline might induce sweating, affecting body odour, thereby leaving chemical cues about emotional states. Stress is known to increase micturition (Smith et al., 2011a) and defecation (Sanger et al., 2000), perhaps promoting the spreading of such olfactory messages. Chronic stress alters immunity at the level of epithelial tissue (e.g. digestive tract or skin), thereby altering the qualitative and quantitative properties of the microbial communities living there and therefore the odorant metabolites they release. Stress odours may thus arise from alterations in the balance of metabolite levels, rather than being the appearance of novel compounds (Sakuma et al., 2013; Bombail et al., 2018a).

A meta-analysis of 26 studies suggests that humans may also be capable of communicating emotional states and detecting stress-related emotions (fear and anxiety) via body odours (de Groot and Smeets, 2017). However, the question of human pheromones is a matter of debate (Wysocki and Preti, 2004) since, although some responses have been identified (some are referenced in de Groot and Smeets, 2017), the vomeronasal organ putatively involved in pheromone detection might only be vestigial in humans (Trotier et al., 2000; Liman and Innan, 2003; Zhang and Webb, 2003). If there is a significant pheromone effect, it is still controversial and human fear might be better communicated via auditory and visual signals.

Attempts have been made to harness some of this knowledge for a few practical applications. Research has been carried out to attempt to regulate the impact of rodent pests to protect agricultural crops and plantations. For instance exposing faecal predator odours (coyote) on sheep and cattle might prevent grazing in certain areas (Pfister et al., 1990). But other aspects of the predator-prey relationship can be explored. Studies of African wild dog (*Lycaon pictus*) in a zoo show that an endocrine stress response can be induced by exposure to prey odour such as gazelle. Not all manifestations of stress are detrimental, it is thought a rise in cortisol levels may also simply reflect arousal caused by a novel situation, and that this could be used for enrichment purposes (Rafacz and Santymire, 2014). There are clearly potential applications and exciting knowledge to be gained from the world of semiochemicals.

4. Can odours be calming and reduce the effect of the stress response?

Although stress is an adaptive response that prolongs life in the wild, it can have negative physiological and behavioural consequences. Several types of substances are available in the pharmacopeia to modulate targets in the endocrine and nervous systems in order to treat pathological manifestations and consequences of chronic, inappropriate or exacerbated stress responses. Pharmacological treatments can sometimes provide relief and reduce anxiety or depression. Beta blockers reduce the effects of adrenal catecholamines and can dampen

physiological and psychological effects of the acute stress response (Middlemiss et al., 1981). Selective serotonin reuptake inhibitors (SSRI, aka Prozac) are reported to reduce in some cases the depressive symptoms, often precipitated by chronic stress (Arroll et al., 2009). We have seen how odours can influence animal mood and behaviour in the case of innate and learnt negative associations. Can odours reduce the stress response and its manifestations? Historically, other cultures with an alternative view of the medical process have used inhalation aromatherapy for the treatment of diverse ailments. Many plant-derived products have remarkable pharmacological effects when used topically or internally, but here I shall solely discuss inhalation of odorant compounds and the treatment of exacerbated stress response by the odorant sensation. The practice is sometimes referred to as aromachology, defined as 'olfactory effects that have been scientifically demonstrated to affect mood, physiology and behavior' (Herz, 2009). Several studies point towards a role for odours in the amelioration of stress effects using various experimental models, and in the following, evidence for and against these claims will be reviewed. It should be added, that the phenomenon is distinct from social buffering where the presence of socially related animals appears to provide anxiolytic effects in experimental animals, a process that (sometimes) involves olfactory cues of animal origin (Kiyokawa and Hennessy, 2018).

Evidence that odours act to attenuate the impact of stress and improve animal mood

Oils extracted from citrus fruits have been a popular source of odorants in stress-relief research. Essential oils from bergamot, *Citrus bergamia*, are reported to have beneficial effects on anxiety and depression symptoms (Navarra et al., 2015). A study in rats describes that bergamot oil inhalation reduced expression of anxiety in behavioural tests and reduced corticosterone level (Saiyudthong and Marsden, 2011). Rats that were exposed to lemon oil vapours showed reduced immobility time in the Porsolt forced swim test (Porsolt et al., 1977), a marker of antidepressant activity (Komori et al., 1995). This reduction in immobility time was confirmed independently in mice (Komiya et al., 2006). Lemon oil also had anxiolytic effects in an elevated plus maze task (Komiya et al., 2006) . In this latter study, lavender and rose oils did not produce any anti-depressant or anxiolytic effects. However, rose oil had anxiolytic effects in rats in another report (de Almeida et al., 2004) and was also shown to reduce the corticosterone induction response (Fukada et al., 2012). Besides essential oils, another odour has been tested in several stress models: a mixture of trans-2-hexenal and cis-3-hexenol called Green Odour (GO), which evokes in humans the smell of fresh cut grass. In models of prenatal stress, application of stressors to gravid dams sometimes leads to depressive-like behaviours in offspring (Fujita et al., 2010). Following 10 consecutive days of restraint stress during the second half of gestation, dams gave birth to offspring that developed abnormal stress plasma markers responses and depressive-like symptoms. A parallel group of stressed dams treated with GO during the stress exposure regimen gave birth to pups that did not develop such stress-related traits (Fujita et al., 2010), suggesting GO countered the effect of restraint stress. In rats, chronic stress for 10 days in a 3-minute forced swim test increased immobility times, a marker of depressive-like states. GO exposure re-established locomotor behaviour, suggesting a loss in learned helplessness and anti-depressant effects (Watanabe et al., 2011). Rats pre-exposed to GO before exposure to stressors (TMT odours or electric foot shock treatment) showed a lower stress response than non-GO exposed conspecifics (Nikaido et al., 2011). Finally, rats subjected to a fear conditioning paradigm aimed at modelling Post Traumatic Stress Disorder (PTSD) display ameliorated symptoms following GO exposure (Nikaido et al., 2016). There are also reports of odour-mediated stress relief in humans. Men and women waiting for their dentist appointment were asked to fill questionnaires about their inner state and emotions while sat in the dentist waiting room, in the unannounced presence or

absence of orange oil, *Citrus sinensis* (Lehrner et al., 2000). Men were not affected by the presence of odours, but female patients reported less anxiety, a more positive mood, and a higher level of calmness. There is anecdotal evidence that odour exposure during therapy sessions can help patients suffering from PTSD (Daniels and Vermetten, 2016).

Critical analysis of the literature

With so many studies in peer-reviewed scientific journals, it seems surprising that the claim of an odorant-based therapeutic strategy for acute and chronic stress relief has not been taken up by a larger fraction of the scientific and medical community. The mechanisms of action are still unclear, yet the claim that odours might have antidepressant and anxiolytic action in experimental animals requires some mechanistic foundation. Components of the GO affected dopamine release in brain slices and PC12 cell culture (Kako et al., 2008; Kobayashi et al., 2010). A great issue here is that these are not olfactory effects, as the cells and tissues were isolated in a dish; these were pharmacology experiments. In a follow up study, rats with brain cannulae that allowed *in vivo* dopamine sampling, were exposed to GO and this induced neurotransmitter release (Kako et al., 2011). Studies in animal models by use of pharmacological tools, showed that exposure to odours modulated dopamine and serotonin release and their receptors *in vivo* (Komiya et al., 2006). However, in all these studies, there is a lack of negative controls (a comparison to other odours that might not have any effect), so it could just be that any odour arousing the animal leads to striatal dopamine release. Modulation of neurotransmitter action would constitute a possible mechanism for odour stress relief, but this has not yet been clearly demonstrated. What would be the mechanical basis for some commonalities in reported effects for such different odours as GO (Fujita et al., 2010), rose (de Almeida et al., 2004) and lemon (Komiya et al., 2006): would the same olfactory detection and stress-regulating brain pathways be activated? These are not the only questions raised by this literature. There are inconsistencies as to what odours have what effect (e.g. rose oil has anxiolytic effects in some reports but not others), and differences in odorous compound volatility are not acknowledged as possible confounding factor (Komiya et al., 2006). Why would the same odorant have differing properties? There are inconsistencies in terms of protocols used: diversity of control odours, e.g. triethyl citrate (Fujita et al., 2010) and butyric acid (Watanabe et al., 2011) or distilled water (Nikaido et al., 2011), diversity of behavioural effects and endocrine endpoints. All these factors make comparisons difficult. Also, it is challenging to preclude the spreading of odour treatments, therefore experiments cannot be fully blind, a requisite for stringent scientific testing. Odorant concentrations are difficult to ascertain from the methodology descriptions and can be difficult to standardise. Sometimes the effect is attained with very high amounts of an odorant, at 10 and 100% odorant saturation in the air (Tashiro et al., 2016). It might be that high doses of odorant in the air can enter the bloodstream and therefore have pharmacological rather than olfactory effects; in this case, a comparison where the compounds are administered by ingestion or injection would be necessary.

In human experiments, such effects of odours could be attributed to the pleasant element of odour exposure, perhaps helping patients dealing with adversity and the awaited loss of control of, for example, sitting in a dentist chair. In PTSD sufferers during a therapy session, pleasant odours might have grounding and calming effects, a distraction from the negative experience of recalling a traumatic event. Experimental odours might simply cover the unpleasant environmental smells (the eugenol from the dentist surgery or dirty cage litter for animals). It could be that in humans, sensory pleasure or aesthetics allow us to face adversity and to be more resilient to stress. The hypothesis that pleasantness acts in stress relief should also be tested in animals, taking into account individual odour preference variability. Could it also be that laboratory animals whose ancestors have not

experienced the outside world for generations feel soothed by smelling the odour of pleasant essential oils or fresh cut grass? A plausible mechanism for the stress relief observed in experimental animals may be that the presence of an odour act as an environmental enrichment during a stressful situation, in an otherwise relatively barren experimental cage (Wells and Hepper, 2017). These alternative explanations ought to be rigorously tested, in order to discriminate between direct (the odorant specifically acting on stress centres) and indirect effects (e.g. masking effect or enrichment, memory recall).

A meta-analysis of six aromatherapy studies failed to detect any treatment effect (Cooke and Ernst, 2000). Massages in conjunction with aromatherapy may have had a positive therapeutic effect, but massage alone also did, and there was only evidence of a very modest transient anxiolytic effect. Again, treatment blinding is impossible and there may have been flaws in study design (Cooke and Ernst, 2000). The Cochrane collaboration concentrates on reviewing medical data through comprehensive large-scale meta-analysis studies, in order to critically assess the efficacy of treatments and promote evidence-based medical care. A recent search through the Cochrane database (www.cochrane.org) failed to find any significant effect of inhalation aromatherapy. The evidence was at best 'equivocal' (if not ineffective) for alleviating suffering in dementia and in labour pain management (Smith et al., 2011b; Forrester et al., 2014). These meta-analyses are not supporting measurable effects of inhalation aromatherapy, but absence of proof is not proof of absence and further research, with adequate and stronger study design, is needed. Human studies are complex, and because these are challenging and costly to conduct, it often leads to low-power studies, which can further cloud the question. There is a strong tendency towards publication of positive results (e.g. practices such as p-hacking,(Head et al., 2015), and several biases can have detrimental consequences in terms of assessing the validity of scientific claims (Ioannidis, 2005), but a number of recommendations have been made (Ioannidis, 2014; Head et al., 2015).

Appeasing pheromones

In addition to the use plant-derived odorant compounds described above, there have been attempts at attenuating the consequences of the stress response using animal-derived volatile molecules with alleged 'pheromone' properties. A few published studies support the efficacy of those pheromones, which are commercially available in numerous formulations, and advertised for use in several farm and pet species, for a large number of indications. In general, those studies consist in using 'appeasing pheromones' (usually synthetic analogue preparations of compounds found on the skin of conspecifics) in a stressful situation using collars or sprays, and identify an effect on stress- or performance-related indicators. A dog appeasing pheromone mimicking molecules found on the mammary area of lactating bitches (composed of myristic acid, lauric acid, pentadecanoic acid, and stearic acid, (Pageat and Gaultier, 2003) was used on Beagle dogs subjected to fear-inducing thunderstorm recordings. This led to a reduction in behavioural fear and anxiety indicators, in comparison to a control group (Landsberg et al., 2015). Appeasing pheromone also appeared to provide relief in newly adopted dog pups, animals fitted with a pheromone collar exhibited fewer vocal signs of distress (Gaultier et al., 2008). However, in another study, dog appeasing pheromone did not have any effect on the behavioural effect of stress, in military dogs experiencing the transition from foster care to military training (Broach and Dunham, 2016). A bovine appeasing pheromone has also been described. Dairy cows who experienced the seasonal transition from an indoor environment to outdoor pastures exhibited a mild decrease in milk production, possibly through the mild stress induced by novelty. Application of bovine appeasing pheromone improved milk production parameters (Osella et al., 2018). At the stressful time of weaning in pigs, exposure to

a compound mixture analogue to sow skin secretion, improved feeding and growth performance within 48h (McGlone and Anderson, 2002). This commercial preparation is made of various fatty acids: hexadecanoic acid, cis-9-octa decenic acid, 9,12-octyladecanoic acid, dodecanoic acid, tetradecanoic acid, and decanoic acid (Pageat, 2001). Interestingly, pigs might also be affected by rabbit-derived odours. A compound produced by the lactating doe (2-methyl-2-butenal, Schaal et al., 2003) had similar effects on pigs as above, food intake and weight gain were improved by compound exposure (McGlone et al., 2017). It should be noted that a pheromone is a signal involved in intraspecific communication, if it has effects within one species, it does not necessarily mean that this molecule has a biological effect on others. If those compounds are indeed a type of semiochemicals (not pheromones), one should question the evolutionary history of chemical communication between rabbits and pigs, and the significance such rabbit-derived compound might have for the recipient. A possibility is that the olfactory properties of the compounds (fatty acid mixtures) are similar, that they activate similar olfactory receptors, and might be appeasing across species because they might be reminiscent of maternal odours, but this remains to be tested. In a meta-analysis of various treatments used against cat urine spraying, a stress-related behaviour, pheromone therapy was found to be effective using secondary outcome measures, albeit to a lower degree of effectiveness than psychopharmacological treatment (Mills et al., 2011). The only systematic study on the effect of pheromone treatment in dogs and cats identified several potential design and data analysis flaws, indicating that out of 14 studies, only one provided adequate proof for treatment efficacy (Frank et al., 2010). Further concerns have been voiced by others about the validity of some of the claims for pheromone efficacy (Hewson, 2014). Commercial success differs from clinical effectiveness and given the large economic interests at stake, the large scale and multi centre, independent assessment of treatment efficacy should be carried out. There is no information available on how those putative pheromone substances might act, improved mechanistic understanding should shed light on this application of olfactory biology.

Overall there is no clear evidence so far to show odour exposure works spontaneously and effectively for stress relief at the population level; However, are there specific phenotypes of individuals for whom this treatment might work? Might this be associated to other variables e.g. stress resilience or olfactory performance? As we have seen above, there is no such thing as a typical stress response, as animals will differ in terms of physiology and life experience. It is perhaps illusory to use 'one size fits all' solutions for such a polymorphic issue as stress relief. Perhaps it would also be interesting to assess whether the alleged spontaneous effects of those substances differ in animals whose olfactory perception might be altered, such as in the stress or mood –related disorders.

Another way to use odours in stress relief?

The lack of solid reproducible evidence warrants caution in generalising this alleged effect of spontaneous odour exposure on stress. Besides the enrichment hypothesis (above), associative learning could provide interesting tools for modulating animal mood. Negative association with an aversive stimulus (e.g. foot shock and odour) that induces a stress response is a well-established tool to study memory and stress biology. Can animals learn to associate a positive emotional state with an odour and can this be used for stress relief? This positive conditioning has been shown in certain cases for pigs (Oostindjer et al., 2011). Young animals whose mothers had been fed flavoured food during late gestation and lactation showed lower behavioural and hormonal signs of stress response upon weaning when the same odour was presented. Likewise, since maternal odour is critical in early life attachment (Beery and Kaufer, 2015), it could be hypothesised that this reminiscence of the maternal environment and early life experience through olfaction might be a mechanism through

which compounds of lactating female origin with putative 'appeasing pheromones' properties might operate to reduce stress, rather than through intra-specific communication with semiochemicals (see above). Critically, one should wonder about the evolutionary pressures having led to the selection for this alleged phenomenon, consisting in chemical signals from the mother to the weaned or adult offspring. One can question whether the conditioning of positive emotions is as strong as the conditioning of negative emotions, given the strong evolutionary drive that favours the latter, for species survival. It would be interesting to study whether other challenging situations can be made less stressful through this seemingly comforting role of odour application. Attempts to associate a positive affective state with an odour are currently underway (Bombail et al., 2018b).

Under the same label of inhalation aromatherapy, aromachology or pheromone therapy, it could be that a lack of critical thinking has led to the conflation of various biological phenomena: an alleged spontaneous olfactory effect on stress relief, environmental enrichment or the recall of positive emotional states. It would be easy to believe that stressed animals can be soothed by odours as easily as it is to light a patchouli candle, and statements such as '(aromatherapy) is a natural way of healing a person's mind, body and soul' (Ali et al., 2015) can be misleading. To quote a great soul music artist 'When you believe in things that you don't understand/Then you suffer/ Superstition ain't the way' (Superstition by Stevie Wonder, 1972). There might be a case for the use of odours in management of adverse and pathological effects of the stress response (e.g. (Salesse, 2017), but a better understanding of the phenomena and mechanisms at play is essential, and this requires further systematic methodological appraisal.

5. Conclusion.

Animal species managed by humans use olfaction and exhibit stress responses. The inner state of animals and their emotions alters their perception, while perceived odours can sometimes affect their mood and well-being. Several fascinating questions and opportunities lie at the intersection between the study of perception and emotions. Some of this knowledge should be incorporated into research and animal care practices, to better improve animal welfare by understanding their olfactory world. Examples have already been described elsewhere (Nielsen et al., 2015a) and some will be reiterated, in the light of what has been covered here:

- If stressed or depressed animals perceive odour differently, then several aspects of olfaction-driven behaviours will be impacted : their appetite or sex drive might be reduced, their social recognition of conspecifics might be altered and this may lead to increased aggression, odour-based parent-offspring recognition might also be affected. Could the use of olfactory cues (e.g. to enrich the environment or train olfactory function) improve those behaviours?
- Stress-related odours could be detected in animal breeding facilities, as a non-invasive indicator. Odours can also provide information on disease and reproductive status,
- Exposure to stress-related or predator odours should be avoided to prevent emotional contagion,
- Olfactory enrichment and possibly appetitive olfactory conditioning could be used as ways to diversify the sensory world of captive species and contribute towards their well being

I am confident this list will be expanded through our creativity and fearlessness to engage in cross disciplinary thinking.

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