General Introduction

The world in which we live is defined by physical parameters which we can perceive with our corresponding sensory systems, but not all beings are sensible to all or the same parameters. Furthermore, sensory systems for even the same physical parameters can entail important differences between different species. Thus, even when all creatures live in the same world, some of us perceive their surroundings ("*Umwelt"*, Uexküll 1909) quite different than others. Integrated studies about the nature of physical parameters, their perception by animals, the provoked behavioural reactions and the neuronal bases of the perceiving systems are of crucial importance to understand how beings other than humans perceive their *Umwelt* and act in it.

In nature odours are used as media spreading information across the environment just as sounds and colours are. Such odour information can be locally restricted or can be spread over a wide area and distance depending on the odour's chemical characteristics (e.g. volatility). Both animals and plants use odours; the ecological bond between the two kingdoms is firmly based on the transfer of olfactory information. Furthermore, odour perception and correct decoding of the information can be vital for all organisms within the animal kingdom, allowing them to perceive the environment and to react appropriately to it (e.g. finding food sources or prey, avoiding predators, finding mating partners). Therefore processes underlying sensory odour coding and subsequent odour information processing by the olfactory system that lead to appropriate behavioural response patterns are of central interest. The goal of this thesis was first to find out what makes an odour specific and differentiable from others, finding the crucial cues which make two odours similar or dissimilar (Chapter I), second, to investigate how background odours alter behavioural odour perception, examining how the components of a binary odour mixtures change such perceptions (Chapter II), and third, to search for neuronal correlates for the alterations found, studying active neuronal brain structures during olfactory stimulation (Chapter III). Based on these results I tried to establish a model to accurately predict odour mixture processing and, finally, to investigate how the neural representations of odours are formed, how they are modified by the presence of other odours, and how they change with experience. At the end, I expect to reach a much better understanding of the mechanisms underlying the olfactory code, which will improve both our understanding of olfactory coding in general and of how complex brain circuits work.

Animals and human olfactory systems constitutes phylogenetically very old structures (Martin & Jessell 1995, Freeman 1999), processing chemical information from the outside world to higher brain structures. Compared to other sensory systems, at least in humans, this sense is unique because olfactory information is first transferred from the olfactory bulb to phylogenetically older brain cortex regions (see below) before reaching the thalamus and subsequently the neo-cortex, a fact that underlines the ancient roots of this system. The phylogenetically very early invention of a chemical sense system and today's striking homology of the basal construction between certain vertebrates and invertebrates (Hildebrand & Shepherd 1997) today allows comparisons and extension of principles found in one class to the others (Davis 2004). The first relay of odour processing circuits, the olfactory bulbs (OB) in vertebrates and the antennal lobes (AL) in invertebrates are situated at the periphery of the central nervous system (CNS), which is a great advantage, because it makes them easily accessible for experimental investigation. Furthermore, discoveries in the mostly simpler and therefore even more accessible systems of invertebrates can help to understand the more complicated ones in vertebrates, and even the human olfactory system.

In insects, odours can be perceived by chemical receptors, typically situated in olfactory cavities or olfactory sensillae on their antennae, which correspond to the receptors in the olfactory mucus in the vertebrate nose. In honeybees, olfactory receptor neurons (ORNs) are housed within the first eight segments of the antennae (von Frisch 1921, Frings 1944). They are organized in groups of 15-30 neurons which each innervate one sensilla placodeum (Esslen & Kaissling 1976). The sensilla placodea are integrated in the antennae's cuticular walls, protecting the ORNs but having minute pores which allow olfactory molecules to enter. Once the molecules are inside the antenna they are absorbed by the lymph and transported to the receptors on the ORNs by odorant binding proteins (OBPs) (Vogt et al. 1999; Danty et al. 1999). Each type of receptor cell has a different perceptive range; some can be narrow (specialists, e.g. receptive to pheromones) and some can be broad (generalists). The question of ORN interactions is controversial, but some weak evidence was found that odour information is already modulated on the level of neurons belonging to one sensilla placodeum (Getz & Akers 1994; but see de Bruyne 1999). The primary ORNs - which each express only a single type of receptors - transport the odour information from the exterior world into the organism (olfactory transduction) to the ALs in insects and in vertebrates to the OBs (reviewed by Hildebrand & Shepherd 1997). Both structures are similarly organized. The receptor cells converge into the antennal nerve and from there to the glomeruli. These glomeruli are structural and functional units, which form the ALs or OBs. The receptor cells

expressing the same kind of receptors converge onto the same glomerulus. The ratio between receptor cells and glomeruli varies strongly within species, but they all show a great convergence of many receptor cells onto a few glomeruli (Hildebrand & Shepherd 1997; Davis 2004). Within the glomeruli the ORNs form synapses with local interneurons (LNs) and projection neurons (PNs), the counterparts of mammalian periglomerular cells (PGs) and mitral/tufted (M/T) cells. The axonless LNs form extensive multi-glomerular connections within an AL (Sun et al. 1997), while the PNs extend their dendrites into one or only a few glomeruli. The structural AL organization and, in particular, the dendrodendritic connections between LNs and PNs enforce the idea of odour information modulation already on the AL level. The PNs transport the olfactory information via their axons to the protocerebral lobes and the mushroom bodies (MBs), information from multiple sensory systems converge in the mushroom bodies (Rybak & Menzel 1993), and activation of behavioural output neurons could be initiated. In mammals M/T cells project odour information from the glomeruli to phylogenetically older, paleocortical areas: the piriform cortex (with major feedback to the OB), the amygdala, the perirhinal cortex and the entorhinal cortex before the information reaches the thalamus (the gateway to the cortex) and the neo-cortex which makes the primary olfactory system distinctive as compared to other sensory systems in mammals (Davis 2004; Stevenson & Boakes 2003). In contrast to insects, the different M/T cells are interconnected by granule cells (GC) and odour information could also be modulated already at this stage. The remarkable homology in design and function of the olfactory nervous system of insects and mammals allows working on relatively simple nervous systems without losing the possibility to compare and extend results to more complex systems.

Honeybees, *Apis mellifera*, have a very good sense of smell and the ability to form olfactory memories, especially when odours are related to an environmental context like the nest and/or food resources (Menzel 1985; Winston 1987; Menzel et al. 1993). In the laboratory, harnessed honeybees can easily be conditioned to single odours and odour mixtures (Bitterman et al. 1983), which can be studied using the olfactory conditioning of the proboscis extension reflex (henceforth PER; Takeda 1961; Bitterman et al. 1983). Naïve, hungry bees respond to sucrose solution stimulation of their antennae with a PER. After pairing an olfactory stimulation with sucrose delivered to the antennae and proboscis, bees learn and memorize that the odour, the conditioned stimulus (CS), anticipates the sucrose reward, the unconditioned stimulus (US), and thus respond with a PER to the odour (Bitterman et al. 1983). Bees provide a relatively simple, accessible olfactory nervous system from which the ALs represent the first relay. Odour information input comes from the ORNs

which possess different sensitivity to different odours. Thus only an ensemble of many active ORNs could precisely encode odour information which reaches the glomeruli and could then be treated by the AL network of LNs and PNs. The neuronal activation patterns of the glomeruli within an AL during odour stimulation are specific and reliable over different animals and multiple presentations (Galizia et al. 1999a; Sachse et al. 1999). Although investigations until now were limited to only the surface of the ALs (25%) the glomerular activation patterns had a strong overlap (especially when having similar molecular structures) but were nevertheless odour-specific. Neuronal activity in the rest of the ALs might enforce and sharpen the discriminability of the odour. The convergence of odour information from thousands of ORNs onto a few glomeruli - as well as the interconnectivity between them by LNs - favours the idea of odour information processing at this level. Such processing would result in differences between neuronal odour input (ORNs) and output (PNs) patterns. Learning could have a major impact on these differences, which could result from experiences with a certain odour (Faber et al. 1999; Peele 2005). However, learning demands a link between the olfactory system and other sensory systems which could perceive additional relevant information, so that positive or negative associations between the olfactory and other information can be made. Additional information for an odour could be the occurrence of a food reward (which is often the case in flowers) which would enforce a positive association between odour and reward. The VUM mx1 neuron (Hammer 1993) is a most potent candidate for such a link between the odour signal and a reinforcing sugar reward in the ALs (Linster & Smith 1997). This neuron is thought to be the putative internal reward system of the honeybee mediating rewarding signals and is potentially the driving force of changes within the neuronal network of the ALs.

Perceptual similarity and generalization between odour stimuli

One way to benefit from environmental information is generalisation (Pavlov 1927; Shepard 1987). Generalisation from one stimulus to another takes place as a learnt behaviour, released not only by a familiar stimulus, but also by an unfamiliar stimulus. Despite the stimuli being different, they are more likely to be generalised if they are perceived as similar. The functional advantage of generalising between similar familiar and unfamiliar stimuli comes from the fact that similar stimuli often predict similar events in the environment crucial for surviving and learning (Ghirlanda & Enquist 2003). Using terms of Shepard's universal law of generalisation, an individual generalises from a familiar stimulus to a novel one, if the latter falls into the "consequential region" of the familiar stimulus, thus being expected to

cause the same consequences for the individual (Shepard, 1987). Generalisation responses to novel stimuli are normally weaker than responses to familiar stimuli and generalisation curves are generally exponential or Gaussian (Blough 1975; Shepard, 1987; Staddon & Reid 1990; Cheng et al. 1997), especially when stimulus dimensions are well-controlled and, in an ideal situation, when stimuli differences arise from only one critical dimension. But besides this, cases of even stronger responses to novel stimuli (Tinbergen 1951; Mackintosh 1974; Enquist & Arak 1998) and asymmetric generalisation curves are possible (Guttman 1965). Two conditions are essential for generalisation; first, animals must be able to perceive and, second, they must be capable of discriminating the set of stimuli. Discrimination is critical for generalisation, which is therefore not a consequence of mistaking a stimulus for another one, but a cognitive process in which the awareness of two different stimuli is needed (Shepard, 1987). In behavioural odour experiments on honeybees (von Frisch 1919; Vareschi 1971; Smith & Menzel 1989; Laska et al. 1999) generalization can be used as a tool to measure similarity between stimuli, high generalization from one odour to the other would stand for high similarity and low generalization for low similarity between odours. Therefore, in this study (Chapter I), I performed behavioural PER experiments with honeybees using a generalization design in which different groups were trained to one of 16 different odours (16 groups in total) and responses to the CS as generalisation responses to the remaining 15 odours were measured (creating a 16x16 generalization matrix). By analysing the results it was possible to access odour similarity and to identify most relevant odour properties responsible for high or low generalisation responses between odours, representing high or low odour similarity.

Overshadowing in odour mixtures

Odour mixture interactions could critically influence mixture perception and learning. The learning phenomenon *overshadowing* (Pavlov 1927; Kamin 1968, 1969) is suitable to investigate within mixture interaction. Honeybees can discriminate and generalize from odour mixtures to single odours and vice-versa (von Frisch 1919; Vareschi 1971; Smith & Menzel 1989; Laska et al. 1999), thus animals were trained with a binary compound of two stimuli A and B (AB+; "+" indicating the presence of a reward) and then tested with the single components A and B. Overshadowing is defined as occurring if the response to one of the components is higher than that to the other (Staddon 1983; Gallistel 1990; Rescorla & Wagner 1972). Within-mixture interactions arising at a central level are assumed to account for the fact that one component overshadows the other. The response of control groups trained

to either component (A+ and B+) is crucial for the interpretation of the responses of the mixture-trained group (Kamin 1968, 1969). Within-mixture interactions leading to overshadowing are revealed if the response to B in the mixture-trained group is lower than the response to B in the group trained to B alone.

Conditioning	Testing
AB +	B
B +	B

Comparison of test responses to B between groups trained to AB and B alone

However, components may also have different saliencies and overshadowing may simply reflect such a difference without the necessity of invoking any interaction between components. For example, such saliencies could be represented by the amount of generalization between the two odours A and B, measurable by comparing generalization responses in the two control groups (generalization responses to B after A training and generalization responses to A after B training, respectively). If generalisation from one odour to the other is significantly different in one control group compared to the other, this could represent higher saliency for the odour which received more generalisation. Therefore, I performed overshadowing experiments (Chapter II) by training different groups of honeybees to 15 binary odour compounds (AB+) and additionally, carried out the control groups for each compound (A+ and B+). In subsequent tests all groups were tested to A, B and AB. By analysing the results I was able to measure stimuli salience and potential component interactions in binary odour compounds responsible for overshadowing effects.

Conditioning	Testing		
AB +	A	B	AB
A +	A	B	AB
B +	A	B	AB

Experimental design, showing the compound group (AB+) and both control groups trained to the single components (A+ and B+) and the test trials which were randomly carried out

Odour coding and processing in the olfactory nervous system

Odours are encoded in spatio-temporal activation patterns in vertebrate OBs (Friedrich & Korsching 1997, 1998; Hildebrand & Shepherd 1997; Rubin & Katz 2001) and invertebrate ALs (Joerges et al. 1997; Galizia et al. 1997, 1998; Sachse et al. 1999; Ng et al. 2002). In honeybees spatial encoding is given by odour-specific glomerular activation patterns at the level of the ALs (Joerges et al. 1997). Such patterns are symmetrical between ALs within an individual bee and constantly reproducible within and between bees (Galizia et al. 1999a; Sachse et al. 1999). An existing atlas of the antennal lobe, resulting from neuroanatomic reconstructions (Galizia et al. 1999b) allows the identification of glomerular activity patterns in this first olfactory relay in the honeybee brain. During odour perception and specific glomerular activation, olfactory information is treated by the AL network, leading to contrast enhancement between patterns for different odours (Sachse & Galizia 2002, 2003). Odour information perceived by receptor neurons converges onto glomeruli in the AL, receptor neurons carrying the same receptors (transmitting the information of the same odour molecules) converge onto the same glomerulus. Glomeruli represent areas of high-synaptic density where ORNs, LNs and PNs meet. GABAergic local interneurones, having a global inhibitory effect on all glomeruli (homogeneous LNs), seem to be responsible for global gain control mechanisms. At least a second population of neurons, PTX-insensitive, which have specific inhibitory inter-glomerular connections (heterogeneous LNs) is involved in the process which seems to be responsible for contrast enhancement between glomerular activation patterns (Sachse & Galizia 2002). Other inhibitory neurotransmitters such as histamine and/or glutamate are possibly involved, too (Sachse & Galizia, 2002; Barbara et al. 2005). The processed information is send to the MBs and the lateral protocerebral lobes (LPL) by PNs via three main tracts, the medial-, mediolateral- and lateral antennocerebral tracts (respectively m-, ml- and l-ACT) (Abel et al. 2001). The MBs are sights of possible first integration of stimuli information from different modalities, because at least odour, optical and mechano-sensory information converge onto these structures (Mobbs 1982; Strausfeld 2002). The role of the LPLs in the olfactory pathway is not well-studied and still needs to be investigated. The AL is the first structure of the olfactory network in which changes in physiological activity related to olfactory learning were found (Hammer & Menzel 1998; Faber et al. 1999; Menzel 1999). Experiments done on the moth *Manduca sexta* (Daly et al. 2004) showed that the association between an odour and a reward caused a recruitment of synapses in PNs at the level of the AL in an appetitive context. Modifications in odour

representation at the AL level after conditioning were also found in the fruit fly, *Drosophila melanogaster* (Yu et al. 2004).

Besides the olfactory codification in spatio-temporal activation patterns over the ensemble of ORNs, LNs and PNs ("across-fiber patterns", Galizia & Menzel 2001) Laurent et al. (2001) proposed fine temporal dynamics in PNs responsible for olfactory coding. Synchronized neuronal activity oscillations seem to participate in odour coding, allowing differentiation of very similar odour stimuli. During the activity evolution of the odour pattern signals (including phases of synchronised oscillations and desynchronized neuronal activity of PN ensembles) for similar odour stimuli they are becoming more and more distinct over time (Laurent et al. 2001). In other words, the identity of a given smell should not be defined only by a group of active and non-active neurones, but also by their specific synchronous activity and activity evolution over time. Stopfer et al. (1997) showed that honeybees conditioned first with an aliphatic alcohol (C) and then tested to the conditioned odour (C), a similar aliphatic alcohol (S) and a chemically dissimilar odour (terpene, D) were able to discriminate between the conditioned odour C and D but not between C and S if the phenomena of synchronized activity in PNs is affected by picrotoxin treatment, thus restraining neuronal oscillations. A control group receiving saline application into the AL was able to discriminate both C from D and, more importantly, easily discriminate C from S. Therefore, Stopfer et al. (1997) suggest that the synchronization of PNs interrupted by the application of picrotoxin seems to be involved in fine discrimination between odours, but not in coarse discrimination. Here, it should be mentioned that picrotoxin has not only an influence on temporal but also an altering effect on spatial aspects of the signals (Sachse & Galizia 2002). Synchronization gives an additional dimension for olfactory discrimination, "time", particularly important as soon as it is necessary to distinguish strong overlapping glomerular activity patterns (Laurent et al. 2001). According to these results, Laurent et al. proposed the existence of individual neurones or groups of neurones downstream from the PNs which would be sensitive to the presence (or absence) of synchronized entries. Déglise's work (2003) contradicts these results: he found some oscillations on the level of honeybees PNs, as Laurent did, but they did not occur as a consistent and reliable coding phenomenon for odours. The uncertainty about an oscillation factor in the encoding of odour information in the olfactory pathway let me focus purely on the activation patterns of PNs in the ALs without using "time" as a coding factor. Odour information processing in the circuits described above is still not completely understood. Trying to clarify basal odour processing and learning, I performed imaging experiments (Chapter III) with naïve and conditioned honeybees using an experimental overshadowing

design formally used in my purely behavioural experiments. The results allowed me to investigate physiological odour mixture activity compared to single-odour activity and the difference between naïve and conditioned animals on the level of the ALs and, more specifically, on neuronal activity in the PNs.

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