

Women In Olfactory Science

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Book of Abstracts

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Human Olfaction #2 / 10**Olfactory associative learning during human sleep: Interplay between sleep stages, slow wave oscillations and behavior****Author:** Anat Arzi¹¹ *Department of Psychology, University of Cambridge, Cambridge, UK***Corresponding Author:** aa913@cam.ac.uk

Recent finding suggests that humans can learn novel information during sleep, and that this information can modulate behavior during wakefulness in a sleep stage-dependent manner. Specifically, new associations learned during non rapid eye movement sleep (NREM) had larger and longer lasting influence on behavior than associations learned during rapid eye movement (REM) sleep. NREM sleep, unlike REM sleep, is rich in slow oscillation and these oscillations promote memory consolidation of information previously learned during wakefulness. We set out to test whether slow oscillations are also part of the mechanism underlying olfactory associative learning during sleep. We recorded electroencephalogram (EEG) during partial-reinforcement conditioning in NREM and REM sleep. On reinforced trials (two-thirds of trials), the conditioned stimulus (tone or odor) was paired with an unconditioned stimulus (odor). On non-reinforced trials (one-third of trials), the conditioned stimulus was presented without an ensuing odor, which enabled us to measure learning without the interference of the unconditioned stimulus. We found an increase in slow oscillations (0.5-5Hz) power following the conditioned stimulus offset in non-reinforced trials during NREM sleep, compared to REM sleep and to a control experiment in which the same stimuli were presented in a random order during NREM. Moreover, during NREM the increase in slow oscillations following the conditioned stimulus offset was significantly larger when the conditioned stimulus was previously paired with an unpleasant odor than with a pleasant odor. This difference was not evident during REM sleep. Our results demonstrate that new associations learned during sleep increased slow oscillation activity during NREM sleep but not during REM sleep. Furthermore, the increase in slow oscillations depended on the unconditioned stimulus properties (odor valence). This work suggests a link between sleep stage dependent olfactory associative learning during sleep and slow oscillations.

Human Olfaction #1 / 17**The role of the chemical senses for eating behavior, in health and disease****Author:** Sanne Boesveldt¹¹ *Department of Agrotechnology and Food Sciences, Human Nutrition, Wageningen University & Research***Corresponding Author:** sanne.boesveldt@wur.nl

Chemosensory perception plays a crucial role in food choices and intake, and thus in maintaining a healthy nutritional status. These sensory aspects of a food are not only drivers of preferences and aversions, but are also important for steering appetite, signalling nutrient content and satiety processes [1, 2]. Illness and concomitant treatment however may lead to changes in smell or taste function and thereby alter flavor perception and eating behavior. I will here summarize the impact of these alterations during prominent illnesses, such as neurodegenerative disease, and cancer and chemotherapy, identify current gaps in knowledge and formulate relevant topics for future research.

1. Boesveldt, S. and C. De Graaf, The differential role of smell and taste for eating behavior. *Perception*, 2017. 46: p. 307-319.
2. McCrickerd, K. and C.G. Forde, Sensory influences on food intake control: moving beyond palatability. *Obesity Reviews*, 2016. 17(1): p. 18-29.

Olfactory receptors, chemical structure and animal models / 6**Considerations on structure-odour activity relationships in humans****Author:** Andrea Buettner¹¹ *Department of Chemistry and Pharmacy, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
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Odor potency and odor character are obviously tightly linked to chemical structure. Numerous studies have shown that specific structural features such as thio groups or aromatic moieties bare a high potential of causing extremely low odor thresholds, and, accordingly, of inducing potent smells. Likewise, specific groups appear to be commonly associated with specific smell character such as ester functions being predominantly associated with fruity impressions, or terpene structures eliciting balsamic or herbal smells.

However, when investigating specific substance groups with regards to their smell impact on individuals, one is astonished to find at times enormous variance in odor threshold levels, and also quite variable smell descriptions reported by different subjects. On first sight one might be tempted to assume that such differences in smell description are primarily related to linguistic issues rather than real differences in smell perceptions. Nevertheless, such questions can be resolved when asking panellists not only to rate their smell impressions for a specific substance but additionally relate the perceived smell to that of other substances; using this approach it is possible to elaborate which substances are perceived by the same person as being similar in smell. Based on such considerations, our group recently performed a number of systematic investigations on structure-odor activity relationships, starting with the synthesis of structurally related odorants belonging to different substance groups, namely odorants theoretically deriving from fatty acid oxidation, terpene-related compounds as well as phenol-, cresol- and guaiacol-derivatives (1-8). Our group further decodes odorants that occur as artefacts in products of a modern world, namely odorless contaminants in any types of pigments, paints, glues and adhesives, polymers and plastics, to name but a few. Based on this comprehensive substance library, we undertake to characterise the smell sensitivity of individuals to specific compounds, and how these are perceived. This not only helps us to decode naturally occurring, yet unknown odorants, but to also form a broader understanding of smell perception in human individuals.

Olfactory receptors, chemical structure and animal models / 8**The Amphibian olfactory system as a model to study neuroregeneration****Author:** Sara Joy Hawkins¹¹ *Institute of Neurophysiology and Cellular Biophysics, University of Göttingen, Göttingen, Germany***Corresponding Author:** sarajoyhawkins@gmail.com

The olfactory system of *Xenopus laevis* tadpole is an optimal model to study the process of neuronal regeneration. Tadpoles are known for their elevated regenerative capacity, and the olfactory system exhibits lifelong cell turnover and a remarkable ability to recover even after severe lesion. By transecting the olfactory nerve we were able to observe and describe the events that occur as a consequence of this method of lesion that targets olfactory receptor neurons. We found that cell death and stem cell proliferation in the olfactory epithelium begin in the first 48 hours following olfactory nerve transection. New olfactory receptor neurons begin to repopulate the olfactory epithelium and show responses to natural stimulants approximately 1 week after nerve transection. Re-innervation of the olfactory bulb by newly formed olfactory receptor neuron axons also begins at this time. Second order neurons in the olfactory bulb, mitral-tufted cells, were found to lose dendritic tuft complexity after nerve transection, and begin to recover complexity 1 week post-transection. The olfactory bulb decreased in volume after nerve transection, due to cell death and de-innervation, beginning to recover 3 weeks after nerve transection, at which point some glomerular responses to olfactory

stimuli were observed. Our results show that the olfactory system of *Xenopus laevis* loses function after olfactory nerve transection, and recovers in approximately 7 weeks. The detailed time-line we have established for the different events that occur during the process of de- and re-generation after lesion shed some light on the factors that influence the successful recovery of a neuronal system, thus creating a foundation for future work in this area.

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Olfaction and food: an unforgettable experience

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Memory is omnipresent in our life. All actions are regulated and influenced by memory, which constantly provides information necessary to manage and resolve the tasks of everyday life. One of the main functions of food memory is to recall previous experiences associated with food. Therefore, it guides food choice and intake. However, we are often unaware of using our memory. Actually, much of the knowledge about food is acquired incidentally, without any explicit attention or learning, and stored implicitly.

The sense of smell is closely linked with memory, probably more than any of our other senses. Starting from the discussion of the processes involved in the memorization of the “higher”(i.e. vision and audition) and “lower” senses (i.e. olfaction, taste and touch), the present talk is aimed to describe how food memory functions in everyday life, how it can be ecologically measured and how it influences food liking, preference and selection. Age- as well as gender-related differences in the memorization of sensory stimuli are presented and discussed.

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Multisensory Integration and Cerebral Reorganization in Anosmia

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Behavioral and neuroimaging studies have demonstrated that auditory and visual sensory loss leads to neuronal reorganization and promotes enhanced abilities in certain aspects of the remaining sensory modality. In contrast, neuronal reorganization and cross-modal compensation in anosmia (olfactory loss) has obtained very little attention. The sparse existing literature provides mixed results and focuses mainly on performance in, and processing of, the spared chemical senses gustation and the trigeminal sense; the few studies focusing on morphology have use voxel based analysis methods and indicate a minor decrease in gray matter volume within olfactory-associated cerebral areas.

Given the olfactory sense dependence on heterogeneous sensory cerebral areas, a fact that makes pronounced neural reprogramming less plausible due to sustained inputs, we hypothesize that loss of olfactory functions might have supra-modal consequences. In this talk, I will provide an overview of findings from our ongoing projects on congenital and acquired anosmia in which we investigate the integration of auditory and visual stimuli via behavior and functional MRI. I will also discuss neuroplastic changes in individuals with acquired and congenital anosmia based on intrinsic connectivity (resting-state fMRI) and morphology (structural MRI) with a focus on cortical areas processing olfactory stimuli and integrating multisensory stimuli.

Olfactory receptors, chemical structure and animal models / 7**From odors to brain: how odor binding is transduced into electrical signals traveling to the brain.**

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The initial steps of olfaction occur in olfactory sensory neurons located in the olfactory epithelium of the nasal cavity of vertebrates. These neurons are responsible for the detection of odorant molecules present in the surrounding environment and the generation of neural signals that are transmitted to the brain. Once an odor molecule binds to a receptor in the cilia of an olfactory sensory neuron, it triggers a transduction cascade that initiates an electrical signal that travels from the sensory neuron to the olfactory bulb. The odor-induced transduction current is due to the activation of both cation and anion channels. It is well known that the calcium-activated chloride channel TMEM16B/ANO2 is highly expressed in the cilia of olfactory sensory neurons, but previous attempts to establish a physiological role in olfaction have been unsuccessful. We have recently found that genetic ablation of TMEM16B results in defects in the olfactory behavior of mice and the cellular physiology of olfactory sensory neurons.

Human Olfaction #1 / 5**Reinforcement by reward enhances discrimination of odor stimuli**

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An odor mixture in comparison to a pure odor might be processed differently, even if the participants are not able to perceptually discriminate them. It is established that participants can learn to discriminate likewise smelling odors in an aversive learning paradigm. Our hypothesis is that perceptual and neuronal discrimination can possibly also be enhanced by using a reinforcing feedback paradigm. In our experiment, all volunteers performed significantly better than chance level in an odor discrimination task, but only a subgroup that was identified using the signal detection theory, showed a significant improvement throughout the task. Comparing neuronal processing of a pure, pleasant lemon odor to a mixture consisting of a lemon odor and caproic acid, we observed increased activation of the left insula and ventral striatum/putamen in the pure odor compared to the odor mixture condition. The subgroup of good performers improved in differentiating the odors with reinforcement and showed a related activation of dorsal anterior cingulate cortex, midcingulate cortex, operculum and primary somatosensory cortex compared to the other group of participants. In conclusion, the mentioned areas are involved in odor discrimination learning, and processing of odors seems to depend on even subtle changes of odor quality.

Human Olfaction #1 / 4**Multisensory influences on olfactory perception during food consumption**

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Identification of familiar food and avoidance of rotten or contaminated food is critical for human survival. While odors play a key role in this perceptual process, surprisingly few studies have studied the neural basis of olfactory influences on object perception.

During this talk I will highlight the integration of odor into the food object perception during two separate stages of the eating process that draw on two distinct sensory pathways: the anticipatory stage, where odors are perceived by sniffing (orthonasally) in combination with a visual image of the food, and the consummatory stage, where the taste of a food object is bound together with the odor that reaches the nose through the passageways of the throat (retronasally).

I will discuss some perceptual phenomena arising from concurrent presentation of semantically matched or mismatched sensory information during food evaluation, and discuss evidence for interdependency of these phenomena.

I will also present some neuroimaging data from simulations of both anticipatory and consummatory stages of food consumption to compare the cortical processes that integrate information during these distinct perceptual stages.

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Pheromones: fashion fad or fact?

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Pheromones –chemical messengers that convey a sender’s state or trait to a receiver –have long been controversial and may be considered more as a marketing tool to sell perfume than a robust scientific phenomenon. However, over the past years empirical evidence has accumulated demonstrating that humans can pick up dynamic states (e.g. emotion, sickness) and enduring traits (e.g. gender, age) from others via the sense of smell with body odor as the carrier of the information. Obvious next questions pertain to the nature and composition of the chemical substrate in body odour that conveys the message (the “odorprint”), and of the role of context and learning in how the message is perceived. I intend to present a framework to help advance our understanding on the role, significance and mechanisms underlying pheromone communication in humans based on De Groot, Semin and Smeets (2017, in press) which may serve as an avenue for future research.

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Signaling mechanisms in the accessory olfactory system

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In most mammals, conspecific chemical communication controls complex behaviors. Information about individuality, social and reproductive status is conveyed by an elusive class of chemical cues –pheromones. The highly reproducible character of pheromone responses offers a unique opportunity to uncover the neuronal basis of genetically programmed behavior. The accessory olfactory system is a key component in rodent conspecific chemical communication. However, sensory detection and coding of socially relevant chemosignals within the vomeronasal organ and downstream brain areas - the accessory olfactory bulb, the ‘vomeronasal’amygdala and the hypothalamus - is

poorly understood. Combining molecular, biochemical, (electro)physiological, and live-cell imaging methods, as well as behavioral techniques in wildtype and mutant mouse models, we have extended existing models of sensory signal transduction in the vomeronasal organ, analyzed aspects underlying the principle coding logic of pheromone detection, and have, thus, shed light on the physiological basis of social behavior. More recently, we have begun to address the physiological signaling mechanisms in the rodent accessory olfactory bulb. Both in and ex vivo approaches from different electrophysiological angles reveal unexpected intrinsic as well as stimulation-dependent mitral cell properties.

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Genetic and demographic influences on odor perception

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Variation in odor perception is well-documented in the human population. Factors such as ancestry, age, gender, and olfactory receptor (OR) genetics influence perception, but the relative contribution of these factors to the perception of individual odors has only been minimally investigated. We examined the contribution of demographic and genetic factors to 276 different olfactory phenotypes in 332 subjects. We first examined the association between the perceived intensity and valence of 68 odors and the genotype of over 400 ORs and found that variation in a single OR frequently associates with odor perception. Using a cell-based luciferase assay, we demonstrate 7 novel cases in which subjects with non-functional OR haplotypes tend to rate the associated odor to be less intense or more pleasant than subjects with a more functional haplotype. For example, genetic variation in OR11A1 explains a large portion of variance in the perceived intensity of 2-ethylfenchol ($r = 0.36$, $p < 0.001$), and subjects with genetic changes that reduce response to 2-ethylfenchol in vitro rated its intensity of to be lower than subjects with a functional haplotype ($F(3,325) = 13.08$, $p < 0.001$). For some olfactory phenotypes, ancestry is more predictive than the genotype of a particular OR. The perceived valence of vanillin significantly correlates with ancestry ($r = -0.28$, $p < 0.001$), in part driven by the fact that self-reported Caucasians rate it as more pleasant relative to African-Americans ($t(150) = -4.35$, $p < 0.001$). We also find that age and sex contribute to variation in olfactory perception to varying degrees. The perceived intensities of nonanal and linalool negatively correlate with age ($r = -0.25$, $p < 0.001$ and $r = -0.23$, $p < 0.001$, respectively), while the perceived intensity of terpineol is significantly higher in males relative to females ($t(288) = -3.40$, $p = p < 0.001$). By building a model with all four genetic and demographic factors, we are able to explain between 10 and 20% of the variance in 14 different odor perception phenotypes.

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A central contribution to individual differences in taste sensitivity

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It is well established that there are individual differences in taste intensity perception resulting from genetic variation in taste receptors or other peripheral taste physiology (ref). Less explored, is the

possible influence of central mechanisms. The strongest evidence for a central source of variation in gustatory sensitivity comes from a study of the relationship between chemical taste and thermal taste; those that are more sensitive to perceiving a sweet sensation after warming of the tongue also rate gustatory and olfactory stimuli as stronger (ref). We propose that modulation of the anterior insula by the amygdala is a neurobiological candidate for the mechanism. Here we test the hypothesis that a central mechanism plays a significant role in individual differences in taste perception. The goal is to develop a model for the neural mechanism responsible for central gain. We perform the following analyses: 1) an ensemble of seed-based connectivity analyses for which we used regions that showed a main effect of taste vs. tasteless, 2) a dynamic causal network model of modulation of anterior insula by amygdala, 3) whole-brain connectivity to identify a “fingerprint” of an ensemble of taste response. We will evaluate which method best predicts an individual’s intensity perception and discuss plans for future validation studies. Funded by NIDCD R01 DC006706 to Dana M. Small.