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Brain Imaging Studies of the Functional Organization of Human Olfaction

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Introduction

It is believed that sensory functions are organized in a hierarchical and parallel manner. The sense of smell differs in several aspects from other senses: odors can immediately elicit emotional evocations, they are remembered after long time and are difficult to label. This raises the question of whether odorous stimuli may be processed differently from the other sensory stimuli. New data from brain imaging studies suggest that this is not the case and that the specific characteristics of the sense of smell can be attributed to the engagement of limbic structures at an early stage in the signal processing. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are useful for studies of olfactory functions. PET is generally preferable for limbic activations (but only in group comparisons), whereas fMRI should be used for single-subject studies.

Imaging of odorant perception

In accordance with the expectations from anatomical data both PET and fMRI studies repeatedly show an engagement of limbic structures during the passive smelling of odors. Most often, the activations cover the amygdala, piriform, orbitofrontal and insular cortex, (Zatorre *et al.*, 1992; Williams *et al.*, 1997; Zald and Pardo, 1997; Sobel *et al.*, 1998, 1999) and show a right-sided predominance. Considering that the olfactory nerve projections to the brain are ipsilateral, we recently investigated whether the observed right-sided lateralization may be due to a more pronounced activation trough the right nostril (Savic and Gulyas, 2000); PET measurements of rCBF were carried out during monorhinal and passive smelling of four odorants which were perceived as non-trigeminal. Independently of the activated nostril, bilateral activations were found in the amygdala and piriform cortex, anterior cingulate, in the left agranular insular cortex and the right orbitofrontal cortex. There was no significant difference in the pattern or degree of activation between the right versus left nostril stimulations. The observed bilaterality of the monorhinal olfactory processing is congruent with the reports from studies with magnetic source imaging (Kettenmann *et al.*, 1997; Sakuma *et al.*, 1997; Ayabe-Kanamura *et al.*, 2002) and suggests existence of functional connections via the anterior commissure. Thus, the monorhinally presented odorants are perceived bilaterally in the brain independently on the side of presentation.

Functional organization of odorant perception

Odorants are capable to immediately elicit different evocations (hedonistic judgements, familiarity judgements) during the perception of odors, which is the most elemental level of odor processing. Indeed, Zald and Pardo (1997) found that unpleasant odors activated left orbitofrontal cortex and left amygdala significantly more than the pleasant odors. Royet *et al.* recently also observed that judgements of emotionally valenced stimuli compared to emotionally neutral stimuli activated left amygdala and orbitofrontal cortex. The left amygdala and orbitofrontal cortex could, thus, represent the circuits specially recruited during an automatic judgment of odor pleasantness, which possibly is more pronounced during presentations of unpleasant stimuli (Royet *et al.*, 2000). The possibility of a parallel processing during odor perception is of particular interest in the view of the current debate on whether odors are encoded only perceptually (as stated by Engen and Ross, 1973), or also semantically. Koenig used an original olfactory priming paradigm to provide evidence for the existence of both modes (Koenig *et al.*, 2000). The authors proposed that perceptual odor representations are stored in an olfactory pattern activation subsystem, whereas semantic odor representations are stored in an associative memory. We recently addressed this issue by comparing the pattern of cerebral activation during passive smelling of familiar and unfamiliar odors. Apart from the different rating on the VAS scale with respect to odor familiarity, the odors were rated similarly for other odor characteristics. In addition to the olfactory core regions, which were recruited during smelling of both familiar and unfamiliar odorants, smelling of familiar compounds involved networks usually attributed to semantic associations (Savic and Berglund, 2004). Thus, depending on the evocations elicited with the particular odorant, perception of odorous stimuli can involve additional areas to the core regions. This suggests that already the lowest level of conscious odor processing may be executed by distributed parallel circuits.

Imaging of higher olfactory functions

How the human brain processes the discrimination, recognition and identification of odors has only recently been systematically explored (Royet *et al.*, 1999; Savic *et al.*, 2000). In a series of PET studies we investigated the pattern of cerebral activation during five different olfactory tasks: Monorhinal smelling of odorless air (AS), monorhinal smelling single odors (OS), discrimination of odor intensity (OD-i), discrimination of odor quality (OD-q) and odor recognition memory (OM). Whereas activations during OS were related to AS, activations during the three odors related tasks (OD-i, OD-q and OM) were calculated using OS as the base-line. This approach enabled us to disentangle odor related from task related regions.

The olfactory functions were processed by common, as well as task-specific regions. OS activated the amygdala-piriform, orbitofrontal, insular, cingulate cortex and right thalamus. Depending on the task, different subsets of these regions were recruited along with other areas: OD-i and OD-q engaged left insula and right cerebellum. OD-q involved, in addition, the thalamus, cingulate, orbitofrontal and prefrontal cortex, the frontal operculum, the right caudate and subiculum; OM did not activate the insula, but instead, the piriform cortex; with exception for caudate and subiculum, it shared the remaining activations with the OD-q and engaged, in addition, the temporal and parietal cortex. Thus, the three olfactory tasks (OD-i, OD-q and OM) recruited also areas outside the OS-regions; some of these 'outside OS-regions' were shared by several tasks, whereas others were task specific. Furthermore, with the increasing complexity of the task, the activated task-associated areas were more and more remotely connected with the OS regions. For example, right cerebellum was activated by all three tasks (OD-i and

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OD-q and OM). The brainstem (mesencephalon) and prefrontal cortex was activated by OD-q and OM, but not OD-i. The OD-q task specifically activated right subiculum-hippocampus and right caudate, whereas OM, the task assumed to pose the highest cognitive load, engaged the right temporal neocortex and parietal cortex, areas which were not activated in any of the other tasks. When testing cerebral activation during familiarity judgements (a function posing similar cognitive load as the odor recognition memory) in relation to odor smelling, Royet *et al.* (1999) found activation of right orbitofrontal cortex and the anterior cingulate, but also of the left inferior frontal and left superior frontal gyri. The two latter regions are, like the parietal and temporal neocortex remotely connected to the olfactory core regions and constitute an additional sign of hierarchical processing of olfactory functions.

The finding that the amygdala was activated already by OS, without an additional enhancement during OM deserves a special comment. Because the amygdala is essential for the emotional valence it is highly probable that an immediate activation of this structure already during the passive perception of odors underlies the common experience that olfactory stimuli produce immediate recall of the emotional valence related to the source of smell. The same mechanism may also explain the long duration of odor memories—the amygdala is closely connected to the hippocampus and enthorhinal cortex, which leads to an emotional enhancement of odor memories and their unique long term retention.

Conclusions

Like the visual, auditory and somatosensory system, the olfactory stimuli seem to be processed in a parallel and hierarchical mode. The special features of odorous stimuli—the immediate association to emotion and episodic memory—are, thus, not explained by a principally different organization of olfactory networks compared to other sensory modalities. Rather, the underlying physiology seems to be that limbic structures, suggested to represent a late stage in the sensory-fugal stream of information, become involved already at the most elemental level of odor processing, odor perception.

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