REVIEW

Lateralization of Olfactory Processes

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Abstract

Over the last ten years, methods of cerebral imaging have revolutionized our knowledge of cognitive processes in humans. An impressive number of papers dealing with cerebral imaging for olfaction have been published to date. Whereas the early works revealed those structures participating in the processing of odours presented passively to subjects, researchers later recorded brain activity when subjects performed specific olfactory tasks based on memory, emotion and identification. From these results, we suggest that there is a dissociation of olfactory processes, with involvement of the right hemisphere in memory processes and the left hemisphere in emotional processes. The review concludes with a summary of how these lateralized processes are consistent with the gestalt-nature of our olfactory perception.

Key words: emotion, familiarity, fMRI, hedonicity, judgement task, lateralization, olfactory processes, PET

Introduction

Human lesion studies since the 1970s have made a substantial contribution to our understanding of the neural substrate participating in the processing of olfaction (e.g. Gordon and Sperry, 1969; Gazzaniga *et al.*, 1975; Mair and Engen, 1976; Risse *et al.*, 1978; Abraham and Mathai, 1983; Eichenbaum *et al.*, 1983; Eskenazi *et al.*, 1983, 1986, 1988; Zatorre and Jones-Gotman, 1991), but it is only since the 1990s that functional imaging techniques have revealed large-scale activation patterns associated with cognitive processes and have thus allowed the identification of the neural networks specifically activated by odours. Since the first studies using cerebral imaging, more than 100 specific papers and several reviews have been published (Kobal and Kettenmann, 2000; Zald and Pardo, 2000; Zatorre and Jones-Gotman, 2000; Brand *et al.*, 2001; Kettenmann *et al.*, 2001; Savic, 2001, 2002).

The purpose of the current review is not to present an overview of this emerging literature, but to focus on a major finding of the data: the lateralization of olfactory processes as a function of the kind of task performed by the subjects. After a rapid presentation of the basic anatomical data, and

the various methods of cerebral imaging, we shall present neuroimaging data acquired at the level of the orbitofrontal cortex (OFC) and amygdala, while attempting to respect the chronological order of both the findings and the evolution of the concepts and ideas. Briefly, findings indicate that most of the first studies showed activation in the right OFC, which has since been associated with the familiarity judgement task. Activation of the left OFC was simultaneously evidenced during both stimulation with emotional odours and when subjects performed a hedonicity judgement task. This lateralization of olfactory processes as a function of the type of olfactory task was further extended to the olfactory primary cortex and the amygdala. It was hypothesized that the familiarity and hedonicity of odours was consistent with our holistic perception of odours, and that the right–left dichotomy of olfactory processes facilitated or contributed to increased survival from an evolutionary point of view.

The olfactory system: anatomical data

A great deal of data has been accumulated on the neural basis of odour processing, both in humans and animals. We

shall only give a brief report of this anatomical data, because a detailed description would be beyond the scope of the current paper. The reader may consult the following reviews for further information (Scott, 1986; Takagi, 1986; McLean and Shipley, 1992; Shipley *et al.*, 1995; Shipley and Ennis, 1996).

From the olfactory receptors located in the superior region of the nasal cavity, axons lead to the olfactory bulb situated under the ipsilateral cerebral hemisphere. The olfactory bulb cells are connected to the primary olfactory cortex by the fibres of the lateral olfactory tract (Shipley and Reyes, 1991). The olfactory cortex comprises the anterior olfactory nucleus, tenia tecta, olfactory tubercle, piriform cortex (PC), anterior cortical amygdaloid nucleus, periamygdaloid and entorhinal cortices (Figure 1). These projections are primarily ipsilateral. Only a few controlateral connections

between both sides of the olfactory system via the anterior commissure have been reported (Shipley and Ennis, 1996). The major subcortical projections of the PC are the thalamus, the hypothalamus and the ventral striatum (Price and Slotnick, 1983). The lateral entorhinal cortex is the major source of afferent input to the hippocampus (Van Hoesen and Pandya, 1975), and the nuclei of the thalamus has further connections towards the OFC and the insular cortex (Von Bonin and Green, 1949; Nauta, 1960; Mesulam and Mufson, 1985). It has also been reported that the PC possesses projections connecting directly with the OFC (Potter and Nauta, 1979; Price *et al.*, 1991). A further characteristic of the olfactory system is that it has a very rich network of centrifugal fibres leading from the PC, the anterior olfactory nucleus, the amygdala, the lateral entorhinal cortex, the hypothalamus, the locus coeruleus and the raphe
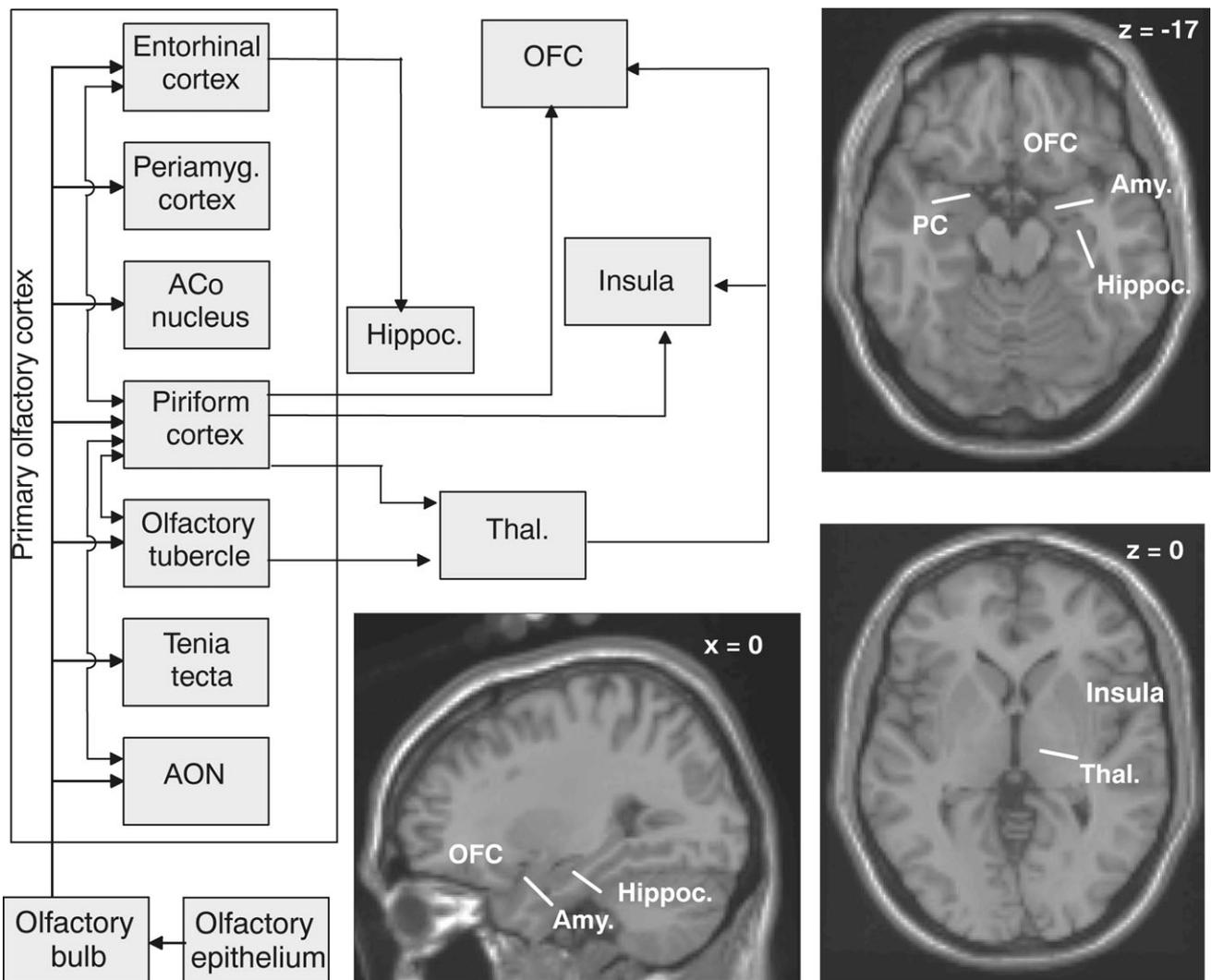

Figure 1 Schema illustrating the major efferent connections of the main olfactory system, and axial and sagittal sections from an anatomically normalized standard brain showing areas of olfactory projection. ACo nucleus, anterior cortical amygdaloid nucleus; Amy, amygdala; AON, anterior olfactory nucleus; hippoc, hippocampus, OFC, orbitofrontal cortex; PC, piriform cortex; Thal, thalamus; x, coordinate in mm along the horizontal line perpendicular to the intercommissural plane; z, coordinate in mm along the vertical line passing through the intercommissural plane (adapted from McLean and Shipley, 1992).

nuclei to the olfactory bulb (Shipley *et al.*, 1995). These fibres enable the brain to control the incoming flow of olfactory signals.

The OFC is heterogeneous and contains several distinct regions that deserve to be described because most cerebral imaging studies systematically activated them (Zald and Kim, 1996a,b; Öngür and Price, 2000; Petrides and Pandya, 2002). Briefly, this description is based on a brain mapping system initially proposed by Brodmann (1909), who parcelled the cerebral hemisphere into more than 50 areas (Brodmann's area, BA). Cerebral imaging studies often refer to these numbered areas to indicate activated areas. Nowadays, the OFC is considered to be a region of cytoarchitectural transition between the agranular and granular cortices of the frontal lobe. Carmichael and Price (1994) proposed a detailed parcellation system to take into account these cytoarchitectural transitions. Very succinctly, the olfactory areas in humans were reported as being the anterior and posterior BA 11 areas corresponding to Walker's areas 11 and 13 respectively, described in the monkey (Walker, 1940). The BA 47 area, just lateral to the BA 11 and also implicated in olfactory processes, was reported to correspond to Walker's area 12.

Methods of cerebral imaging

Non-invasive functional neuroimaging methods are commonly classified into two broad groups: electromagnetic techniques, such as electro-encephalography (EEG), event-related potential (ERP) and magneto-encephalography (MEG); and haemodynamic techniques, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

Electromagnetic techniques

In the field of olfaction, classical methods utilizing EEG and ERP recordings in response to olfactory stimuli have been in use since the 1960s (e.g. Allison and Goff, 1967; Smith *et al.*, 1971; Kobal, 1982; Lorig *et al.*, 1988; Kobal and Hummel, 1991a,b; Kobal *et al.*, 1992; Hummel *et al.*, 1995; Pause *et al.*, 1996; Castle *et al.*, 2000). The MEG technique has been in use since the 1990s (e.g. Kobal and Hummel, 1991b; Tonoike and Kaetsu, 1995; Kettenmann *et al.*, 1996; Sakuma *et al.*, 1997; Kobal and Kettenmann, 2000; Hamada and Yamaguch, 2001). Electromagnetic techniques have excellent temporal resolution (a few milliseconds), but poor spatial resolution (several centimetres). Furthermore, although the magnetic techniques convey information about slightly deeper brain structures with less distortion than using scalp techniques, electromagnetic methods are mainly designed for recording superficial brain activity and are therefore unsuitable for recording small olfactory areas located deep in the brain. This limitation explains the small number of studies devoted to olfaction based on such techniques. Another special electrophysiological method is the stereo-EEG (SEEG) technique that consists in recording intracerebral EEG and ERP activities in epileptic patients using deep electrodes prior to surgical treatment for relief of intractable seizures. Since activity in olfactory areas can then be directly recorded in deep cerebral structures, this method is more suitable for our purposes than the previous ones, but only two studies have been performed to date (Hudry *et al.*, 2001, 2003).

Haemodynamic techniques

In addition to the last method described above, haemodynamic techniques of cerebral imaging such as PET and fMRI are quite suitable for studying olfactory information processing. These techniques allow investigation of the neural activity and metabolism by measuring changes in the regional cerebral blood flow (rCBF) (Cabeza and Nyberg, 2000). rCBF is a good indicator of neural activity, but the resolution of haemodynamic measurements is limited both temporally and spatially. Temporal resolution is limited by the 'sluggishness' of the haemodynamic response: although a neural event lasts a few milliseconds, the rCBF can last for 10 s. In addition, whereas PET cameras possess a relatively good mapping resolution (5 mm), spatial resolution is limited by smoothing applied to the data to improve the signal-to-noise ratio (from 10 to 20 mm). Finally, PET does not usually allow an adequate signal to noise ratio to be obtained in <1 min, although Silbersweig *et al.* (1993) demonstrated detection of PET responses in only 30 s. To study cognitive processes, the radioactive tracer $H_2^{15}O$, which has a half-life of 2 min, is commonly used. Its short half-life allows the planning of several experimental conditions in a single session, commonly up to 12 scans of 60 s each.

fMRI measures rCBF changes through changes in blood oxygenation. When a cerebral region is activated, the concentration of oxyhaemoglobin increases, while that of deoxyhaemoglobin decreases. Deoxyhaemoglobin contains uncoupled electrons responsible for magnetic interactions that do not exist in oxyhaemoglobin, causing a dephasing of the spins in the brain voxel. During activation, spin dephasing is slower and signal intensity is enhanced (a few percent) on a T_2^*-weighted image. This effect is called the 'blood oxygenation level dependent (BOLD) contrast' (Ogawa *et al.*, 1990). The temporal resolution of fMRI is limited by the intrinsic time constant of the haemodynamic response, although images can commonly be acquired in 100 ms. Although epoch designs from 30 to 60 s (Yousem *et al.*, 1997; Sobel *et al.*, 1998b; Royet *et al.*, 2003) are commonly used in olfaction, event-related designs may also be used (Gottfried *et al.*, 2002a,b; Anderson *et al.*, 2003; Gottfried and Dolan, 2003).

Relative to PET scanning, fMRI presents several advantages. It is non-invasive and less expensive because it does not need an infrastructure with a radionuclide-producing cyclotron with its intendant specialized medical and paramedical personnel. fMRI provides both structural and func-

tional information and enables event-related paradigms. Subjects can be scanned several times allowing single-subject analyses not easily conceivable using PET. Lastly, it is quicker to perform, and more commonly available. However, fMRI also has its disadvantages. It is very noisy and is more sensitive to both motion and susceptibility artefacts especially in the vicinity of air–tissue interfaces (Frahm et al., 1988). Because these artefacts are located in the olfactory regions, several methods have been developed to alleviate them (e.g. Liu et al., 1993; Yang et al., 1997; Zald and Pardo, 2000; Wilson et al., 2002). However, these techniques have had varying degrees of success, and at best have shown only moderate signal quality in the ventromedial prefrontal cortex.

To reveal activation patterns the analysis techniques commonly applied in PET and block-design fMRI are primarily based on the principle of the subtraction of images; for example, subtracting images obtained in the baseline condition from those acquired when the subject performs a cognitive task. Before performing analyses, several pre-treatment steps are performed on each subject data set including realignment, stereotactic normalization, and smoothing. Group statistical analyses based on the Generalized Linear Model are then performed (Friston et al., 1995a,b). The specific location of the activated regions is often expressed in the form of three-dimensional coordinates as defined in the atlas published by Talairach and Tournoux (1988). Other more recent atlases are, however, available to identify activation regions (Duvernoy, 1991; Mai et al., 1997).

Statistical maps of the whole brain are exploratory and are used when no a priori hypothesis has been made concerning the neural network involved. It is possible to limit analysis to small anatomical regions of interest (ROI) such as the amygdala or the PC (Zald and Pardo, 1997; Royet et al., 2000, 2001; Kareken et al., 2001; O'Doherty et al., 2001; Gottfried et al., 2002a,b). The analysis of these ROI is more sensitive than maps from a statistical viewpoint, and notably overcomes the problem of variability in location and size across subjects, but can more easily give false positive responses. Statistical maps and ROI are most often used as a complement to other methods of data acquisition.

The orbitofrontal cortex

The first noteworthy study using the bolus H_2O technique to measure rCBF during PET scans in healthy subjects was described by Zatorre et al. (1992). They found that the two most significant foci were located at the junction of the temporal and inferior frontal lobes in both hemispheres, corresponding to the PC. The third focus was located in the right OFC (corresponding roughly to BA 11), and the fourth one in the left inferior medial frontal lobe (BA 25). They suggested that 'the asymmetric activity in OFC is related to more complex analyses of stimulus properties that preferentially recruit right hemisphere mechanisms'.

Activation in the right OFC (or more activation in the right than left OFC) was corroborated in most subsequent studies using both PET and fMRI techniques (Koizuka et al., 1994; Levy et al., 1997, 1998; Small et al., 1997; Sobel et al., 1997, 1998a, 2000b; Yang et al., 1997; Yousem et al., 1997, 1999; Fulbright et al., 1998; Francis et al., 1999; O'Doherty et al., 2000; Savic and Gulyas, 2000; Zatorre et al., 2000). Such a consensus in results is striking, and is consistent with most of the data found in behavioural studies in healthy subjects and lobectomized patients (Toulouse and Vaschide, 1900; Rausch et al., 1977; Abraham and Mathai, 1983; Zucco and Tressoldi, 1988; Cain and Gent, 1991; Zatorre and Jones-Gotman, 1991, 2000; Jones-Gotman and Zatorre, 1993; Kobal et al., 2000; Bratko and Barušic, 2002). It was additionally observed that the right OFC was activated independently of the stimulated side, although the right OFC rCBF was higher during right nostril stimulations (Savic and Gulyas, 2000; Zatorre et al., 2000). Savic and Gulyas (2000) concluded that 'odours seem to be processed both ipsi- and controlaterally, with a right hemisphere preponderance irrespective of the stimulated nostril'. Rather than BA 11, it appears that the most likely location for the observed activation is a more posterior region (within area 13), strongly connected with the PC and amygdala (Zald and Pardo, 2000; Zatorre and Jones-Gotman, 2000). This cytoarchitecturally distinct area is not described in the Talairach and Tournoux atlas, but appears to be structurally homologous to Walker's area 13 in the monkey (Walker, 1940) and has been identified as an olfactory area in humans by Beck (1949) and Petrides and Pandya (1994). If any, such an asymmetry of olfactory processes found in humans can be related to structural, morphological and neurochemical asymmetry previously evidenced in olfactory structures in animals (Prasadao Rao and Finger, 1984; Heine and Galaburda, 1986; Dluzen and Kreutzberg, 1996; Rodriguez-Gomez et al., 2000). Furthermore, it is not unique because lateral asymmetries in perception of complex stimuli have also been reported in the auditory, visual and somesthetic modalities (Bryden and Bulman-Fleming, 1994). While a left-hemispheric dominance is commonly observed for language function, stimuli such as musical sounds, faces or visuospatial material require processing mechanisms mainly involving the right hemisphere (McKeever and Hulling, 1971; Rizzolatti et al., 1971; Zatorre, 1979).

Zald and Pardo (1997) reported the first noteworthy exception to the strong asymmetry described above. Measuring rCBF with PET when exposing healthy subjects to highly aversive olfactory stimuli (i.e. dimethyl sulphide, ethanethiol, methanethiol), they observed strong rCBF increases in the left OFC, but also in both amygdalae. This result was the second outstanding finding in olfactory neuroimagery.

Parallel and hierarchical processing of odours

In the first studies using cerebral imaging, odours were passively presented to subjects. In addition, some authors selected odorants considered to be the most neutral, difficult to name, unfamiliar, and similar in intensity ratings (Zatorre *et al.*, 1992; Savic *et al.*, 2000). It has however been emphasized that 'The presence of a "passive" task in an activation paradigm ignores the nature of the cognitive components of such a task and therefore obscures the interpretation of any observed between-task differences in brain activity' (Démonet *et al.*, 1993). From concepts deduced from cognitive psychology (Craik and Lockhart, 1972; Craik and Tulving, 1975; Kosslyn and Koenig, 1992), we suggested the use of various olfactory tasks to study different odour processings (Royet *et al.*, 1999, 2001). Cognitive studies have shown that sensory stimuli can be analysed at different levels, ranging from simple sensory analysis to deep or semantic analysis. In his review of the literature on odour memory, Schab (1991) suggested that the process of olfactory identification varies 'in informational specificity from pleasantness and familiarity judgements to single-label, object-name identification, with various intermediate steps'. We further assumed that the detection task requires a superficial judgement not involving stored representations of odours, that perceptual and semantic odour representations are stored in separate neural subsystems, and that edibility judgements can involve the activation of semantic odour representations. We have thus shown that superficial processing of odour detection induced only a weak rCBF increase in the right OFC of healthy subjects, whereas the familiarity task, requiring perceptual processing, showed more activity in this area. In contrast, activity was significantly higher in the left OFC during the hedonicity judgement task.

Furthermore, we have shown that high-level odour processing, namely the edibility and familiarity judgement tasks, involves the left inferior frontal gyrus (BA 47) for semantic associations (Royet *et al.*, 1999). Given that both these judgements are strongly correlated with naming, we concluded that activation of this area is also likely to reflect naming. This interpretation has been corroborated by more recent studies showing activation of this area to be correlated with familiarity ratings (Savic and Berglund, 2004), and during odour identification (Kareken *et al.*, 2003). Our work has further revealed the involvement of the visual cortex when subjects performed edibility judgements (Royet *et al.*, 1999, 2001). Activation of visual areas has also been found by other authors (Qureshy *et al.*, 2000; Suzuki *et al.*, 2001; Gottfried, personal communication). Given the well-known difficulty of verbalizing and identifying odours, we claimed that visual areas might participate in the semantic processing of odours, in the sense that subjects might visualize the object evoked by the odour and determine, for example, if the odour evokes an edible item.

From our cerebral imaging data, we suggested that odour processing comprises both a *serial processing of information* from the primary to secondary olfactory cortices, and a *parallel, distributed processing* depending on the nature of the cognitive operations being performed (Royet *et al.*, 1999, 2001). The pattern of activation in the left and right OFCs varied respectively depending on whether the odour processing was related to emotional response (hedonicity judgement) or recognition memory (familiarity judgement).

Other cerebral imaging studies have been based on the use of active tasks such as detection, discrimination, recognition memory and identification (Dade *et al.*, 1998, 2002; Qureshy *et al.*, 2000; Savic *et al.*, 2000; Zatorre *et al.*, 2000; Kareken *et al.*, 2001; Suzuki *et al.*, 2001). In many of the aforementioned studies, several structures have also been found to be activated in addition to the OFC, such as the amygdala, hypothalamus, entorhinal, cingulate gyrus, thalamus, insula and cerebellum. On the basis of the different olfactory tasks, Savic *et al.* (2000) thus showed that odour perception activates complex neural networks which include all these structures, but in a variable way depending on the task. For example, they showed a significantly higher activity in the lateral OFC, frontal operculum and brainstem during odour quality discrimination and memory than during single odour exposition and intensity discrimination, whereas all four tasks activated structures in the olfactory cortex and more closely related structures. They further showed a higher activity in the right temporal neocortex and right parietal cortex during odour memory than in odour quality discrimination. From these findings, Ivanka Savic and her colleagues suggested that olfactory functions are organized in both *a parallel and hierarchical manner*, depending on the character and complexity of the task

A lateralized and extensive emotional circuit

In their pioneer study, Zald and Pardo (1997) demonstrated that exposure to a highly aversive odorant produced strong rCBF increases in the left OFC and both amygdalae, whereas exposure to less aversive odorants produced rCBF increases only in the left OFC. Furthermore, the activity within the left amygdala was significantly correlated with subjective ratings of perceived aversiveness, but not with perceived intensity. In a subsequent noteworthy work, applying covariance analyses to their previously acquired PET data, Zald *et al.* (1998a) estimated the functional connectivity between the amygdala and OFC in both hemispheres. They found a significant correlation between rCBF increases in the left amygdala and OFC in response to aversive odorants relative to when attempting only detection of an odour. Only the left OFC and amygdala operated in unison when exposed to an unpleasant odorant. The authors interestingly added that 'if functional coupling reflects an active process that facilitates the interaction or communication between regions, functional uncoupling may optimise neurocognitive functioning by isolating the processing in

different regions'. These findings stressed for the first time the dynamic nature of connectivity between the amygdalae and OFCs in olfaction.

In a more recent work, we examined the neural correlates of responses to emotionally valenced olfactory, visual and auditory stimuli using PET and found an extensive emotional network (Royet et al., 2000). For all three sensory modalities, emotionally valenced stimuli led to increased rCBF in the OFC, temporal pole and superior frontal gyrus in the left hemisphere. These findings suggested that pleasant and unpleasant emotional judgements call upon the same core network in the left hemisphere regardless of the sensory modality. This core network was, however, activated in addition to a number of circuits specific to individual sensory modalities. Emotionally valenced olfactory and visual, but not auditory stimuli thus produced additional rCBF increases in the hypothalamus and the subcallosal gyrus. Only emotionally valenced olfactory stimuli induced activation in the left amygdala, suggesting that such stimuli are more potent activators of the amygdala than visual and auditory stimuli.

A major result found in the three PET studies described above was the strong involvement of the left hemisphere in emotional processes. This finding was consistent with data found in other PET or fMRI studies of chemical senses (Zald et al., 1998b; Royet et al., 2001, 2003; Gottfried et al., 2002a; Anderson et al., 2003), but also with other types of emotional processing such as the subjective experience of anger, dysphoria and obsessive-compulsive symptoms (Drevets et al., 1992; Pardo et al., 1993; Rauch et al., 1994; Morris et al., 1996, 1998; Dougherty et al., 1999). Interestingly, hemispheric lateralization of olfactory-mediated affective processes is not restricted to human beings and has also been observed in rats. Left bulbectomized rats are impaired in their response to emotionally negative social odours (Dantzer et al., 1990). Such a lateralization has, however, never been reported by Rolls and his team in their numerous electrophysiological studies on the functions of the OFC in monkey (for review, see Rolls, 2004). Overall, this data indicates that left hemisphere structures play a more prominent role in emotional processing than could be explained by traditional accounts of the lateralization of emotions. It is indeed noteworthy that studies based on behavioural, lesion and electrophysical precepts have attributed a decisive role to the right hemisphere in emotion (Ahren and Schwartz, 1985; Gainotti, 1989; Jones and Fox, 1992; Wittling and Roschmann, 1993). This does not appear true when performing cerebral imaging studies. On the one hand, the previous works on behavioural, lesion and electrophysiological data were not devoted to the study of olfactory processes, and it is possible that the present results reflect a specific aspect of olfactory function. On the other hand, it is conceivable that methodological bias in neuroimaging could also explain the present data.

When a neural network implicated in an emotional response to odours is located in the left hemisphere, then the structures pertaining to this network do indubitably play a slightly different role. In a recent fMRI study, we demonstrated that actively performing the hedonicity judgement task for pleasant and unpleasant odorants compared to passively smelling these same odorants specifically induced more activation in the left OFC (Royet et al., 2003). It follows that this area is implicated in the conscious assessment of the emotional quality of odours and that the OFC activation in Zald and Pardo (1997) subjects, who passively detected mildly aversive or pleasant odorants, was probably evoked by spontaneous hedonicity judgements. In contrast, the piriform–amygdala region did not appear to participate in conscious evaluation but was activated in relation to the emotional intensity (faculty to cause arousal) of the odours. Several recent distinct findings in relation to the primary olfactory cortex and the amygdala however deserve a more detailed presentation.

The primary olfactory cortex and the amygdala

Although activation of the PC has been found in several studies in humans (Zatorre et al., 1992; Small et al., 1997; Sobel et al., 1998a, 2000b; O'Doherty et al., 2000; Savic et al., 2000; Kareken et al., 2001, 2003), several subsequent studies reported either no piriform activity (Yousem et al., 1997; Zald and Pardo, 1997; Dade et al., 1998, 2002; Fulbright et al., 1998; Royet et al., 1999, 2000, 2001; Zatorre et al., 2000; Suzuki et al., 2001), showed only inconsistent activation (Sobel et al., 1998a; Yousem et al., 1999) or associated these activations with sniffing (Sobel et al., 1998a). These discrepancies were partly explained by the finding that odorants induce sharp increases in PC activation which then rapidly habituates despite continued odorant presentation and detection (Sobel et al., 2000b; Poellinger et al. 2001). Since in previous fMRI studies the odorants were presented for a relatively long time, habituation limited responses in the PC. Despite this phenomenon, different roles were attributed to the piriform–amygdala region. We will successively examine the various propositions.

A memory and familiarity judgement processor?

Dade et al. (1998, 2002) examined human brain function using PET during different stages of olfactory memory processing: (i) encoding of new odours; (ii) recognition of odours after a short interval and (iii) recognition of odours after a long interval (24 h). They did not find PC activation in the encoding condition, but found a weak bilateral activity in the short-term recognition condition, and strong bilateral activity in the long-term recognition condition. They added that these findings were in agreement with the theory developed in several studies (Haberly and Bower, 1989; Bower, 1991; Hasselmo and Barkai, 1995), 'which suggests that the primary olfactory cortex serves as a type of associative memory system, which allows for the association

of odour stimuli with memory traces of previously experienced events'. Several findings lend support to the theory that the PC is involved in learning and memory. For example, long-term synaptic potentiation was shown to occur in the rat PC *in vitro* (e.g. Jung *et al.*, 1990) and *in vivo* at the conclusion of learning (Roman *et al.*, 1993; Litaudon *et al.*, 1997b). The finding that PC activity changes in rats after odour learning may explain the greater piriform activation during recognition than in encoding. In Dade's study, the greater piriform activity during long-term recognition could reflect increases related to memory consolidation processes.

It is well established that recognition of a repeated stimulus may depend on two different forms of memory processes (Mandler, 1980; Lehrner *et al.*, 1999; Bogacz *et al.*, 2001). According to the 'dual process theory', these forms are called 'familiarity', which is based on perceptual processing, and 'recollection', which includes the retrieval of contextual information. Familiarity judgements are made on the basis of a feeling, without specific information about the encoding episode, and thus relate to implicit or unconscious memory. In other terms, familiarity ratings to a large extent reflect the clarity of perceptual processing (Broman *et al.*, 2001). Recollection is seen as a form of an elaborate or conceptually driven process, and thus relates to explicit or conscious memory. Since a familiarity judgement task is thus clearly associated with a memory recognition task, it was surprising that we did not observe any activation in the PC in our previous PET studies. In a recent fMRI study (Plailly *et al.*, 2003), we were, however, able to show that the odour familiarity judgement task also specifically activated primary olfactory areas such as the right PC.

We further showed activation of the PC only in the right hemisphere. Although Dade *et al.* (2002) reported bilateral activation of the PC, careful examination of their data indicated a more substantial activation in the right than left PC and showed that the extent of this spread in the right OFC was fairly wide. Findings with brain-damaged patients are convergent with these data. For instance, findings on the recognition of abstract visuospatial designs in unilateral temporal lobe epilepsy patients indicated that left-lesioned patients give more 'known' (familiarity process) than 'remembered' (recollection process) responses, whereas right-lesioned patients depict the opposite pattern (Blaxton and Theodore, 1997). Lastly, it has been demonstrated that the right prefrontal cortex is specialized for familiarity-based traces, whereas the left prefrontal cortex is specialized for recollective memories (Kensinger *et al.*, 2003).

A hedonic intensity and arousal processor?

In a recent fMRI work, we examined those networks separately activated by pleasant and unpleasant odours while subjects rated their degree of pleasantness or unpleasantness by using the 'finger-span' technique (Royet *et al.*, 2003). Subjective intensities of odorants perceived by subjects were checked and found to be identical between pleasant and unpleasant conditions. When we subtracted images obtained in the pleasant condition from those obtained in the unpleasant condition, we mainly observed activation of the left amygdala–piriform region and ventral insula. No activation was observed with the 'pleasant–unpleasant' contrast. Electrodermal and plethysmography responses were also recorded to control for covert physiological manifestations of the emotional response. We demonstrated that subjective hedonic perception (rating of degree of pleasantness or unpleasantness) was stronger with unpleasant than pleasant odours and that individual subject variations in electrodermal amplitudes were correlated with finger-span ratings. Unpleasant odours therefore induced stronger emotional responses than did pleasant stimuli, independently of perceived subjective intensity. Other concomitant data have consistently shown that the BOLD signal in both the amygdala (Anderson *et al.*, 2003) and the PC (Rolls *et al.*, 2003) is related to odour intensity, but not to odour valence. Interestingly, a similar dissociation of the neural representation of intensity and affective valuations was found in gustation (Small *et al.*, 2003; see also the preview by Anderson and Sobel, 2003). We have emphasized that, to manipulate odour valence, Anderson *et al.* (2003) had selected an intensity range that provided rather neutral odours and that their data then suffered from a restriction of affective range (Royet *et al.*, 2003). In our study, the odours selected to be at the extremes of unpleasantness were therefore perceived as more intense and were more likely to evoke a much stronger emotional reaction than the pleasant odours (Royet *et al.*, 2003). Although we agree with Anderson's results that amygdala activation is independent of valence, the first point to be underlined is that the strength of the emotional response, i.e. emotional intensity (even more specific with unpleasant odours), is determinant for activation of the amygdala. The second point to be emphasized is the preferential involvement of the left amygdala in the negative emotional processing of olfactory stimuli. This result is consistent with previous findings (Zald and Pardo, 1997; Zald *et al.*, 1998b) and has also recently been reported by Gottfried *et al.* (2002a). Specifically considering the PC, these same authors found bilateral activation elicited for all odours regardless of valence. It is also worth noting that in the visual domain, the responses of the amygdala to unpleasant stimuli are almost always left lateralized (e.g. Morris *et al.*, 1996; Lane *et al.*, 1997; Phillips *et al.*, 1998; Taylor *et al.*, 1998; Whalen *et al.*, 1998; Pessoa *et al.*, 2002). We explained the activation of the piriform–amygdala region observed for strongly emotional, so rather negative, stimuli in our study from the level of arousal that they induced. 'Arousal refers to the extent to which stimuli are calming (low arousal) or activating (high arousal) and this dimension has been described as being orthogonal to the valence dimension' (Zald, 2003). Preferential activation of the amygdala in response to negatively valenced stimuli

further appears to be a general principle, since it is observed far more consistently than activations induced by positively valenced stimuli (Breiter *et al.*, 1996; Hamann, 2003).

Functional heterogeneity within the PC and the amygdala

Attribution of a distinct function to the right and left PC and amygdala is made more complex by the fact that these structures are subdivided from an anatomical point of view, and therefore can also subtend different functions. Lateralization of olfactory processes could then involve only one part of these structures. In animals, a functional dissociation between the anterior and posterior parts of the PC has been shown by anatomical as well as optical and electrophysiological recording studies (Litaudon *et al.*, 1997a,b; Mouly *et al.*, 1998; Chabaud *et al.*, 2000; Haberly, 2001). Notwithstanding the 'sniffing versus smelling' dichotomy evidenced by Sobel *et al.* (1998a), Gottfried *et al.* (2002a) were the first authors to show functional heterogeneity within the PC in humans. They showed that the posterior PC mediates basic odour perception (so neutral odour) and detection. In this regard, the posterior PC activations described in their study were situated close to those identified in previous imaging experiments using passive smelling (e.g. Zatorre *et al.*, 1992; Savic *et al.*, 2000; Sobel *et al.*, 2000b; Poellinger *et al.*, 2001). In contrast, they found that the anterior segment of the PC is receptive to hedonic quality, especially at extremes of odour valence. They also noted a difference in temporal processing according to whether odours were pleasant or unpleasant.

Although Anderson *et al.* (2003) found that the amygdala response is not specifically related to the dimensions of the positive and negative valences of olfactory experience, the amygdala comprises several subnuclei, and thus a 'collapse' across these subdivisions could have blurred the segregation of pleasantness coding. To guard against this possibility, they tested this, but did not find any functional heterogeneity within the amygdala for hedonic valence. The whole amygdala response profile appeared characteristic of smaller subdivisions. Functional segregation of the posterior amygdala was found by Gottfried *et al.* (2002b) with appetitive, but not aversive olfactory learning. As noted by the authors, these findings were intriguing and the reverse pattern of results could have been predicted. Gottfried *et al.* (2002b) suggested that the use of unpleasant odours could cause insufficient arousal to engage amygdala-dependent conditioning and/or that the reactions of disgust provoked by unpleasant odorants could activate the amygdala only poorly. These hypotheses, however, appear inconsistent with findings described in previous sections and data from a recent study in which disgusting odours induced strong activation in the amygdala (Wicker *et al.*, 2003).

Regarding functional heterogeneity within the PC and amygdala, too little data has been published to be able to draw conclusions. The proximity of areas such as the PC and amygdala, and *a fortiori* of subregions of these areas, can in addition lead to the misinterpretation of activation patterns. The question is indeed whether the fMRI technique can allow the functional dissociation of small adjacent regions. To date, it seems that the event-related fMRI technique associated with analyses of small ROIs enables the examination of such subregions of the PC and amygdala. Recording of intracerebral EEG activity in these structures could also be an alternative method adapted to evoking responses. If subtle differences in function are implied in subregions of the PC and amygdala, it is likely that new investigations will soon allow us to elucidate their specific role.

Conclusions

Zatorre *et al.* (2000) claimed that 'data suggest a need to revise the traditional view of PC as a simple sensory relay in a hierarchy'. However, neurophysiologists have long since established that the primary olfactory cortex is a cortex involved in highly integrated processes (see Haberly, 2001, for review). Cells in the PC do not respond to only olfactory input, but also fire vigorously in relation to the non-olfactory components of an odour discrimination task (Schoenbaum and Eichenbaum, 1995). The findings described above further subtend this assertion, and prove that the primary olfactory cortex in humans also participates in high levels of processing. It appears that the primary olfactory cortex has several roles and that these different functions can probably be ascribed to different subregions. With improvement in cerebral imaging techniques, it is likely that we may soon be able to distinguish activation patterns in substructures of this cortex such as the anterior olfactory nucleus, olfactory tubercle, frontal and temporal parts of the PC and the diagonal band nucleus as already shown by Sobel *et al.* (2000b). In summary, it was found that both odorants and sniffing activate the PC. This double function is coherent given that 'sniffs may be regarded as the attentional spotlight of olfaction' (Sobel *et al.*, 2000b). In addition to this 'zoom lens' function, the PC further appears to participate in memory processes such as long-term recognition memory (Dade *et al.*, 2002) and familiarity judgement (Plailly *et al.*, 2003) and to the evaluation of hedonic intensity (Gottfried *et al.*, 2002a; Royet *et al.*, 2003). Furthermore, these processes seem lateralized with the preferential involvement of the right PC in memory processes and the left PC in hedonic intensity. The hedonic aspect (quality) further appears to be processed in the anterior part of PC, whereas odour detection seems to be processed in the posterior part (Gottfried *et al.*, 2002a).

Lateralization of odour processing

Several theories have been proposed regarding the hemispheric asymmetry of cerebral processing. The HERA model, for instance, suggests that the left prefrontal cortical regions are more involved during the learning of new material (encoding), whereas the right prefrontal cortical regions are supposed to be more involved during subsequent

recall or recognition (retrieval) (Tulving *et al.*, 1994; Habib *et al.*, 2003). However, the relevant anatomical regions within the extensive prefrontal cortex were not specified. It has been hypothesised that the right hemisphere is better at 'holistic' or 'global' processing, and the left hemisphere at 'local' processing (Fink *et al.*, 1999). Regarding left–right lateralization of the amygdala activity, other hypotheses have been suggested such as unconscious versus conscious processing of stimuli (Morris *et al.*, 1998), innate versus conditioned fearful stimuli (Dolan and Morris, 2000), and cognitively learned fear versus experimentally learned fear (Phelps *et al.*, 2001), respectively.

Findings reported in the field of olfaction demonstrate that basic perceptual processes appear lateralized between the hemispheres, not only at the level of the OFCs, but also in primary olfactory regions including the PC and amygdala. It appears that the right hemisphere participates in the process of recognition memory, whereas the left hemisphere participates in the emotional processing of odours. First, these distinctions probably reflect more functional asymmetries than fully fledged dissociations. Second, since these two processes are closely related and difficult to dissociate, most studies simultaneously observe activation patterns in both hemispheres. Consistent with this, and although evidence suggests that each hemisphere can function independently (Gordon and Sperry, 1969), it is the interaction of the two that allows for optimal performance in more complex olfactory processing. The specificity of each hemisphere is all the more difficult to show as the airflow periodically reverses between both nostrils (Hasegawa and Kern, 1977) causing a slightly different image of the olfactory world to be conveyed to the brain (Sobel *et al.*, 2000a), and that gender and handedness may also interact with hemispheric lateralization (Royet *et al.*, 2003).

Several studies indicate that the right hemisphere is involved in the processing of pleasant odours. For instance, Zatorre *et al.* (2000) studying neural mechanisms involved in odour pleasantness and intensity judgements, demonstrated activation in the right OFC only. The lack of activation in the left OFC could, however, be explained by the use of moderately familiar odours. Intensity, hedonicity and familiarity have indeed been reported to be closely related, and less familiar odorants are rated as rather neutral and not intense (Distel *et al.*, 1999; Royet *et al.*, 1999). With the exception of pyridine, the odorants used in Zatorre's study were not very intense and, since activation was summed on 60 s, the unpleasant dimension could then be eclipsed to the detriment of the pleasant dimension. Anderson *et al.* (2003) corroborated that activation in the left OFC showed greater responsiveness to unpleasant than pleasant odours, but also claimed that activation in the right medial OFC was greater for pleasant than unpleasant odours, regardless of intensity. The preferential activation of the right caudolateral OFC was subsequently replicated with pleasant tastes (Small *et*

al., 2003). Activation of the right PC with pleasant odours was also reported by Gottfried *et al.* (2002b). Recent behavioural studies have finally indicated that subjects stimulated through the right nostril provided higher hedonic scores than those stimulated through the left nostril (Herz *et al.*, 1999; Dijksterhuis *et al.*, 2002) but it appears that the authors used rather neutral or pleasant odours. Briefly, from these data, we suggest that the right hemisphere is activated by pleasant odours because these are less emotionally arousing, and that cerebral processing of the familiarity rating is then engaged or prominent. This hypothesis could be tested by performing a comparative cerebral imaging study, in which subjects judge either hedonicity or familiarity of the same set of odours selected *a priori* as being rather neutral or pleasant. We suppose that activation patterns would be more lateralized in the right hemisphere for the familiarity than hedonicity judgement task.

The dichotomy of unpleasant versus pleasant emotional responses for odorous stimuli is not associated with the respective functions of left and right olfactory systems as has been suggested in several studies. Whereas the specialization of the left hemisphere for higher cognitive processes such as language is indubitably well established (Gazzaniga, 2000), it appears that the basic perceptual processing of odours is also lateralized between the hemispheres, with hedonic judgements (and emotional intensity) and familiarity judgements being lateralized in the left and right hemispheres respectively. Objections have been raised that the wide network activated in the left hemisphere for processing olfactory emotions (Royet *et al.*, 2000) may be partly due to the influence of semantic processing. This viewpoint is supported if we refer to the OFC and superior frontal gyrus, but such an explanation cannot be corroborated by data concerning activation in the PC/amygdala, temporal pole and insula. Furthermore, it would be surprising that top-down semantic processes activate a wide neural network in the left hemisphere after stimulation only with emotional odours. Even when odours are presented passively and are not emotional, subjects are probably performing an implicit task of semantic processing. Interestingly, Zald (2003) also brilliantly pointed out the problem of emotional lateralization in a wider context by stressing that the neuroimaging data on the amygdala fails to support traditional models generally deduced from lesion data. He emphasized that role of the right amygdala was probably more important to the successful recognition of facial emotion. In other words, it appears that the right amygdala is more involved in recognition than emotional processes.

It appears that lateralization of the olfactory system hinges on three principles: one being based on 'analytical' processing (semantic), the second and third based on the 'non-analytical', basic perceptual processing, i.e. emotional and familiarity processings. The left brain would participate not only in analytical processing, but would also be processing the hedonic value of odours. The right brain

would be 'non-analytical', 'holistic', and would process the familiarity of odours. Hedonic value as well as familiarity levels are crucial, decisive determinants of odour identity. A right-hemispheric advantage in processing odour familiarity and a left-hemispheric advantage in aversive or unpleasant odour processing enable a better and faster basic reaction of the 'flight/fight/fear type', because they can contribute to increased survival from an evolutionary viewpoint. A familiarity processing is unaware of the details of a stimulus and induces a feeling of 'known' before more semantic processing can be performed. Similarly, 'emotional processing takes place irrespective of details of a stimulus, often before detailed properties can even be perceived or inferred' (Kunst-Wilson and Zajonc, 1980; Zajonc, 1980). The 'aversive' term includes toxic food odours, stress odours that can be related to fear, odours of fire, dangerous fumes and polluted environments and natural gas leaks. If, in all these situations, the aversive or unpleasant aspect induces an arousal reaction, it also involves a very rapid decision as to whether or not an odour is familiar. It thus appears that temporal factor is a key component in hedonicity and familiarity judgements. It should be interesting to measure response times of subjects and take them into account in analyses. Activation patterns associated with these dimensions could then be strengthened.

Conclusions

To date, cerebral imaging findings have shown that olfactory function involves a complex and extensive olfactory neural network. Odour processing appears to be based on two main modes of processing, a serial processing with successive involvement of the primary and secondary olfactory areas, and a parallel processing (right hemisphere versus left hemisphere) depending on the nature of the cognitive task. While areas located in the right hemisphere such as the OFC and PC are more involved in memory and familiarity ratings, those located in the left hemisphere, such as the OFC, insula, PC, amygdala, temporal pole and superior frontal cortex, participate more in the emotional response to odours. These different structures would, however, be involved at different levels of emotional olfactory processing. Whereas the piriform–amygdala region appears to be associated with the evaluation of emotional intensity and therefore more activated with unpleasant than pleasant odours, the caudolateral OFC appears to mediate a conscious assessment of these odours. The role of the superior frontal cortex would be to control one's own emotional state in the making of personally relevant decisions.

In humans, our difficulty in verbalizing and/or identifying odours is consistent with the *Gestalt*-nature (i.e. unitary) of our olfactory perception, and the shortened olfactory input-to-cortex pathway of the olfactory system. Wilson and Stevenson (2003) claim 'that early analytical processing of odors is inaccessible at the behavioral level and that all

odors are initially encoded as "objects" in the piriform cortex', i.e. that *odour percepts are synthetic*. Familiarity/ novelty and hedonicity perceptions can represent components of this *holistic perception* and their rapidity of execution represents an unquestionable advantage for survival. The PC has been reported to involve a detector of novelty (Sobel *et al.*, 2000b), and the familiarity-based signal may be similar to that required for determining whether an object is novel (Kensinger *et al.*, 2003). The major finding reported in the current review from neuroimaging studies is likely right–left lateralization of these processes. Although rarely described in animal studies, this lateralization of perceptual processes appears highly consistent with data obtained from cerebral imaging studies in fields of research other as olfaction. In order to formally test these hypotheses that are only derived from neuroimaging results, it would nevertheless be of further value to study patients with lateralized lesions in olfactory regions by testing them on specific judgement tasks

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