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REVIEW OF THE LITERATURE

Olfactory system and emotion: Common substrates

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Summary
The aim of the review: A large number of studies suggest a close relationship between olfactory and affective information processing. Odors can modulate mood, cognition, and behavior. The aim of this article is to summarize the comparative anatomy of central olfactory pathways and centers involved in emotional analysis, in order to shed light on the relationship between the two systems.
Anatomy of the olfactory system: Odorant contact with the primary olfactory neurons is the starting point of olfactory transduction. The glomerulus of the olfactory bulb is the only relay between the peripheral and central olfactory system. Olfactory information is conducted to the secondary olfactory structures, notably the piriform cortex. The tertiary olfactory structures are the thalamus, hypothalamus, amygdala, hippocampus, orbitofrontal cortex and insular cortex.
The impact of odors on affective states: Quality of life is commonly impaired in dysosmic patients. There have, however, been few publications on this topic.
Emotion and olfaction: common brain pathways: There are brain structures common to emotion and odor processing. The present review focuses on such structures: amygdala, hippocampus, insula, anterior cingulate cortex and orbitofrontal cortex. The physiology and anatomy of each of these systems is described and discussed.

Introduction

Odor may be defined as a particular sensation elicited by the action of certain chemical substances on the olfactory system. Olfaction is the function whereby odors are perceived.

There is no consensus as to the definition of emotion. According to the standard French dictionary ''Larousse'', an emotion is ''a sudden disturbance or transient agitation caused by a strong feeling of fear, surprise, joy, etc.''. Some authors focus on its affective dimension, others on its physiological and behavioral aspects (''tendency to act''). Neuroscience classifies emotions as simple or secondary. An emotion is said to be simple or primary if accompanied by universal facial expressions or gestures, independently

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of upbringing and culture. A complex emotion, also called secondary or mixed, results from the combination of several simple emotions. In an attempted description of emotions, Ekman et al. [1] reduced the number of simple emotions to six: joy, sadness, fear, anger, surprise and disgust. Examples of secondary emotions would be nostalgia, love, hatred, etc. Neuroanatomy clearly distinguishes between emotional feeling and emotional consciousness, the two being under the control of distinct structures [2].

A number of scientific studies have focused on the relationship between emotion and odor. The connections between the two have been used by many authors in the classical and contemporary literature [3]. Physiologically, olfactory stimuli are processed according to their emotional content, even when any emotional context is lacking. Like emotions, odors may be given positive (appetitive), negative (aversive) or neutral valence. These close connections, which all of us encounter in everyday life, are related to cerebral substrates common to the two. The present review aims at a synthesis of the anatomic and functional relations between the worlds of olfaction and emotion.

The olfactory system: anatomic bases

On the in-breath, odorant molecules pass through the nasal cavity: this is called air transport. They may also be transported retronasally. Reaching the olfactory neuroepithelium, they cross its covering mucous film [4]. Transport proteins (olfactory binding protein) secreted by Bowman's glands help carry certain hydrophobic olfactory molecules [5,6].

The olfactory neuroepithelium covers the inferior side of the cribiform plate of the ethmoid bone, the superior part of the septum and the medial side of the medial concha. It is composed of three types of cell: olfactory neurons, support cells, and basal cells underlying the olfactory stem cells. The primary olfactory neurons have a bipolar architecture with a basal axonal pole and an apical dendritic pole. They are constantly being renewed from the basal cells. Transduction occurs in the primary olfactory neurons, ''translating'' the chemical message into nerve impulse emission frequencies. The dendrite ends in a swelling with numerous hair cells carrying the olfactory receptor proteins of the G-protein-coupled transmembrane segment 7 receptor family. These chemoreceptor proteins include receptor sites of various shapes, so that a given odorant molecule can be recognized by several different types of protein. The axons, originating in the basal pole of the primary olfactory neurons, are gathered in bundles of some hundred fibers in an envelope of glial cells known as ''sheath cells''. These guide the neurons, the constant renewal of which innervates the olfactory bulb in a targeted manner [6].

The olfactory bulb is the first relay in the olfactory system; it comprises about 8000 glomeruli, which receive the primary olfactory neuron axons [7]. All messages from sensory neurons expressing a given receptor protein converge on a single glomerulus. This strong convergence enables low-intensity signals to be detected. The image of an odor in the olfactory bulb is made up by all the glomeruli corresponding to the various receptor proteins activated by the odor. The efferent (mitral) glomeruli cells transmit this information to the piriform cortex. There is thus an authentic map of neuronal activation, known as the glomerular odotopic map [6].

The axons of the olfactory bulb mitral cells successively cross the olfactory peduncle and olfactory tract before projecting onto the primary olfactory cortex; the information processed in the piriform cortex then projects to various brain areas: the orbitofrontal cortex, amygdala, hypothalamus, insula, entorhinal cortex and hippocampus [8]. As we shall see, these areas are also involved in many emotional functions. Anatomically, the primary olfactory cortex consists mainly of the piriform cortex (or gyrus ambiens) and periamygdalar cortex, both composed of archeocortex [9]. The mitral cell axons terminate in the superficial layer of the piriform cortex, synapsing with pyramidal cell dendrites to form an excitatory/inhibitory network. The secondary olfactory cortex receives fibers from the primary olfactory areas, and is situated mainly in the insula and entorhinal cortex, the input area of the hippocampus attached to the parahippocampal cortex. Functionally, odor intensity is associated with piriform cortex [10] and amygdala [11] activity, while the orbitofrontal cortex is involved in odor identification and olfactory memory [12,13].

Functional brain imaging study of the affective dimension of odors (their pleasantness or unpleasantness) gives contradictory results. Zald and Pardo [13], using positron emission tomography (PET), associated aversive stimuli with amygdala and left orbitofrontal cortex activation, and more pleasant stimuli with piriform cortex and right orbitofrontal cortex activation. Levy et al. [14] explored the cerebral substrate of this affective dimension on functional magnetic resonance imaging (fMRI). Olfactory stimulation induced orbitofrontal cortex, entorhinal cortex and anterior cingulate cortex activation, but independently of valence. Fulbright et al. [15] explored brain activation for pleasant and unpleasant odors in 30 healthy subjects, and found dorsal anterior cingulate cortex, prefrontal cortex, precentral gyrus and insula activation; only pleasant odors induced right precentral gyrus and left anterior cingulate cortex activation. Anderson et al. [6] found amygdala activation to be associated with odor intensity but not valence, whereas orbitofrontal cortex activation was associated with valence independently of intensity; they, like others [16], suggested that the experience of pleasure depends on prefrontal cortex integration functions [11]. Finally, the amygdala seems to be a strategic locus where olfactory and neuroendocrine stimuli are integrated, modulating feeding behavior [17].

Classically, the olfactory cerebral areas are divided into two types:

- neocortical (e.g., orbitofrontal cortex), providing conscious odor perception;
- limbic (e.g., amygdala), underlying the affective component of pleasant or unpleasant odor.

As we have seen, this distinction is too simple to take account of all the data of functional brain imaging, but it does at least underline the fundamental affective dimension of odor perception. This affective dimension is reflected anatomically in the similarities between the cerebral substrates of olfaction and emotion.

Table 1 Comparison of anatomy of olfactory and emotion-linked systems (first two columns). Involvement in two pathologies (depression and schizophrenia) possibly related to olfaction.

	Olfaction	Emotion	Depression	Schizophrenia
Olfactory bulb	+		+	+
Amygdala	+	+	+	+
Hippocampus		+	+	+
Piriform cortex	+			
Entorhinal cortex	+		+	
Anterior cingulate cortex	+	+	+	+
Insula	+	+	+	+
Orbitofrontal cortex	+	+	+	+
Central gray nuclei			+	+
Planum temporale				+
Superior temporal lobe			+	+
Corpus callosum			+	+
Parietal cortex				+

In bold: Structures studied in this paper.

Emotional impact of olfactory disorder

Despite the high rate of olfactory disorder in the general population and the large number of clinical studies of dysosmia, very little research has been done on the functional impact of olfaction loss. Quality of life is severely impaired in a large proportion of dysosmia patients with respect to safety, eating habits and interpersonal relations. Dysosmia patients often experience depressive mood disorder or major depression episodes. Systematic studies, however, are rare. Deems et al. [18] compared a series of 374 patients with olfactory disorder and 362 control subjects matched for age and gender: the former had significantly higher beck depression index (BDI) scores than the latter; however, no means of categorical diagnosis was proposed. In a series of patients with olfactory disorders (hyposmia, anosmia, parosmia) secondary to acute rhinitis, Faulcon et al. [19] found that almost 60% showed some degree of depression during the first months of olfactory impairment; no significant differences emerged according to type of olfactory disorder. Faivre [20] observed nine anosmic patients followed up in the community over an 11 month period, and reported that ''anosmia had induced signs of vital disinvestment''. This disinvestment was expressed at an olfactory level, with aversion to perfume and tobacco smoke during the period of anosmia and revival of interest in perfume once the anosmia was cured.

The relative lack of assessments of emotional impact, and particularly of the incidence of major depression in anosmic subjects, means that, while certain psychological effects of anosmia have been described, the field largely remains to be explored.

Emotion and olfaction: common cerebral substrates

More than any other sensory modality, olfaction is like emotion in attributing positive (appetitive) or negative (aversive) valence to the environment. Certain odors reproducibly induce emotional states [21,22], and emotional induction modifies odor perception [23]. Certain cerebral substrates are in fact common to emotional and olfactory processing, and this may account for the olfactory disorders encountered in psychiatric disorders such as depression or schizophrenia [24,25]. We shall successively review the functions of the amygdala, hippocampus, insula, anterior cingulate cortex and orbitofrontal cortex (Table 1).

Three brain systems can be schematically distinguished: reptilian complex, limbic system and neocortex. The reptilian complex is phylogenetically the oldest of the three, comprising the brainstem and central gray nuclei; rich in opiate receptors and dopamine, it controls the instinctive behavior necessary for survival, such as feeding and defending territory. The limbic system surrounds the reptilian complex, and comprises subcortical (amygdala, hippocampus) and cortical structures (parahippocampal cortex and cingulate cortex); it plays a central role in emotional regulation and memory. The neocortex is phylogenetically the most recent, covering the cerebral hemispheres and underlying perception, action and cognition.

Amygdala

We have seen that the piriform cortex projects onto the orbitofrontal cortex indirectly, via the amygdala. Functionally, odor intensity is associated with amygdala activation [11], as is response to aversive stimuli. The amygdala is also a strategic bridge integrating olfactory and neuroendocrine stimuli to modulate feeding behavior.

One essential function of the amygdala is rapid, sometimes non-conscious, detection of emotional signals, especially of threat. Closely connected to the hippocampus, the amygdala plays a key role in emotional memory: i.e., enhanced memory performance for events associated with emotion [26], including emotions elicited by odor [27]. The amygdala complex is located anteriorly, superiorly and medially to the head of the hippocampus and comprises several gray-matter nuclei composing two main structures: the medial and the basolateral amygdala. Phylogenetically, the medial amygdala is the older and evolved from the olfactory system to extend its threat-detection capability to

other sensory modalities [28]; it is essential in the perception and expression of fear [29]. Activation recruits brain centers involved in anxiety symptoms: hypervigilance and vegetative symptoms. The basolateral amygdala receives multiple sensory afferents, which take on a negative valence as they are processed; its activity can be regulated by the prefrontal cortex during subjective awareness of emotion.

The amygdala plays a major role in the physiopathology of affective disorder, both anxiety and depression. In social phobia, for example, amygdala activation is stronger than in normal subjects in response to faces expressing anger compared to neutral faces, especially in the implicit condition (when the emotional content of the stimulus has not been explicitly processed) [30]. In depression, the amygdala seems to be hyperactive at rest [31]. There is also hyperactivation in response to negative stimuli, even when not consciously perceived (subliminal presentation). This hyperactivation tends to normalize with antidepressant treatment, whether the emotional stimuli are consciously perceived or not [32]. Finally, in case of genetic predisposition to anxiety or depression, increased amygdala activity is observed for negative (faces expressing fear or anger) compared to matched neutral stimuli [33].

Hippocampus

We have seen that the secondary olfactory cortex is located mainly in the insula and entorhinal cortex, the hippocampus input area. Olfactory stimulation was reported to lead to activation of the entorhinal cortex, but independently of valence [11].

On the medial face of the temporal lobe, the fifth temporal circumvolution is part of the limbic system. It comprises the hippocampus above and the parahippocampal gyrus below, separated by a transitional area called the subiculum. The hippocampus is composed of two mainly parallel open tubes: Ammon's horn and the enclosed dentate gyrus; it shows great neuroplasticity, and is phylogenetically older (archeocortex) than the adjacent parahippocampal neocortex. It plays a fundamental role in long-term memory, response to stress and contextualization of emotional experience. The entorhinal cortex is part of the parahippocampal gyrus, but is the main hippocampal input structure, a pathway along which information converges to be memorized.

The hippocampus is one of the most widely studied brain structures in the physiopathology of depression. Two independent MRI meta-analyses found it to be smaller in depressed patients [34]. It also plays a critical role in autobiographical memory, which is impaired in depressed subjects, even in remission [35]. The notion that the hippocampus should be smaller in depressed subjects fits with that of neuroplasticity, which is central to the physiopathology of depression. It is noteworthy that early damage to the entorhinal cortex, the ''entrance'' to the hippocampus, may account for the early olfactory disorder found in Alzheimer's disease [36].

The insula

We have seen that the secondary olfactory cortex receives fibers from the primary olfactory areas, and is mainly located in the insula and entorhinal cortex. Exploration of brain activation to pleasant and unpleasant odor stimuli finds activation of the insula [16].

Apart from its role in olfaction, the insula is involved in processing aversive emotion and in integrating bodily sensation in the assessment of emotional status [37]. It is invisible from outside the brain, on the floor of the fissure of Sylvius. Covered by the frontal, parietal and temporal opercula, which form its edges, it constitutes the fifth lobe of the brain and also includes the primary taste area. In network with the neocortex, limbic system and central gray nuclei, it plays an important role in the perception of intrusion signals such as disgust and pain, contributing to unifying their sensory and emotional dimensions [37]. It also plays a role in social cognition: relating observation of the reactions of others (mimicry, movement) to associated emotional experience, it underlies the affective resonance component of empathy.

The anterior cingulate cortex

We have seen that the anterior cingulate cortex, also known as the limbic lobe, is activated by olfactory stimulation; according to some reports, this activation is independent of valence [6], while according to others the anterior cingulate cortex is activated only in response to pleasant odors [15].

The cingulate cortex is visible on the medial face of the cerebral hemispheres. It is the bridge between the reptilian and the prefrontal cortex and surrounds the corpus callosum from the hippocampus to the orbitofrontal cortex. In network with the precuneus on the medial face of the parietal lobe, the posterior cingulate cortex is involved in self-consciousness and processing of signals bearing personal meaning [38]. The anterior cingulate cortex is involved in detecting conflicts of attention; it underlies the emotional dimension of physical pain and moral pain and social distress in situations of separation or exclusion [39].

The orbitofrontal cortex

We have seen that the piriform cortex projects onto the orbitofrontal cortex directly or indirectly via the amygdala. The olfactory contingent of the amygdala projects onto the orbitofrontal cortex. Functionally, the orbitofrontal cortex is involved in odor identification and olfactory memorization [12,13]. According to certain authors, aversive stimuli are associated with left and more pleasant stimuli with right orbitofrontal cortex activation; according to others, olfactory stimulation elicits orbitofrontal cortex activation, but independently of valence [40].

Anteriorly to the central sulcus (fissure of Rolando), the frontal lobe is in close relation with the thalamus and central gray nuclei via five frontal-subcortical-frontal loops, which regulate the frontal lobe's motor, oculomotor, cognitive, emotional and motivational functions. Posteriorly to anteriorly, the frontal lobe comprises the motor cortex, controlling movement, the premotor cortex, which prepares movement, and the prefrontal cortex. The prefrontal cortex is the most anterior part of the brain, constituting one-third of the human cortex. It has no sensory afferents or

motor efferents, but integrates information preprocessed by the associative sensory areas and the limbic system. Schematically, the prefrontal cortex can be divided in three: dorsolateral, orbitoventral and medial.

The dorsolateral prefrontal cortex underlies short-term memory and executive functions (planning, mental flexibility, inhibition). It takes the subject beyond immediate perception, enabling projection in time [41] and, in network with the hippocampus (involved in long-term memory), suppression of undesirable memories [42]. In network with the central gray nuclei, the medial prefrontal cortex supports motivation; it enables anticipation of reward and self-initiation of action. Medial prefrontal cortex lesions induce apathy and even akinetic mutism. In network with the posterior cingulate cortex, it also plays an important role in social cognition: it underlies self-representation, attribution of emotional valence to odors [16] and personalization of emotion.

The prefrontal orbitoventral cortex, or orbitofrontal cortex, comprises the inferior side of the superior, medial and inferior frontal convolutions and the gyrus rectus (the most medial) and secondary olfactory cortex (the most posterior). Connected to the limbic system by the cingulate cortex, it processes the somatic markers of the autonomic nervous system associated with emotional context [43,44] and integrates emotion into cognition in decision-making [43]. It subordinates reptilian system fixed action patterns to rules established by the dorsolateral prefrontal cortex. Orbitofrontal cortex lesions induce errors of judgment and personality disorders such as acquired sociopathy [43].

Conclusion

The close anatomic relations between the systems deployed for olfaction and for emotion account for the important links found between these two functions. These findings suggest that the study of olfaction/emotion interaction is worth pursuing. Olfactory disorders are regularly found in case of depression or schizophrenia [24,25]. This association may be explained by brain disorders associated with depressive and schizophrenic symptomatology (Table 1) [25]. Some of these brain areas play a role in processing both emotion and odor.

Conflicts of interest statement

None.

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