

Olfaction – A Window to the Mind

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Olfaction and its relation to neurological and mental disease is a field of growing interest. The sense of smell can provide a natural window to the brain. This window provides an opportunity to examine neural mechanisms and brain function in a non-invasive way. Analysis of brain function has been enhanced in recent years by technologies such as functional magnetic resonance imaging and the ability to record other electrophysiological outputs. We review the current understanding of the relation of olfaction, mental health and autoimmunity.

STRUCTURE AND FUNCTION OF THE OLFACTORY SYSTEM

The odor sensory organ comprises a unique sensory organ that can detect many thousands of scents based on only very minute airborne concentrations of a chemical substance. Hearing, vision, and touch are stimulated by frequencies of sound, light and pressure in a predicted linear manner. Odorants have no obvious connection with each other except that they are molecules that can evoke sensations in the olfactory system. Odorant molecules must be small enough to be volatile so that they can vaporize and therefore are limited to the range of 200–400 Da, but within that range there is an infinite number. The olfactory system has solved this by generating a huge number of individual receptor genes, which in fact constitute the largest gene superfamily in the vertebrate genome. Among the mouse genome, about 3% of the genes code for olfactory receptors [1]. Interestingly, humans have about 900 olfactory receptor genes, but 63% are non-coding (called pseudo-genes) [2]. Although humans, with their reduced dependence on smell, still have 300 active olfactory receptors genes, the visual system needs only two genes to detect the color spectrum [2]. The olfactory system comprises a sensory organ (the olfactory epithelium and bulb) and specific olfactory brain regions (the primary and secondary olfactory cortex).

THE OLFACTORY EPITHELIUM AND BULB

The olfactory mucosa is specialized for the detection of odorants and consists of the olfactory epithelium and its underlying

lamina propria. Unusually, the olfactory epithelium undergoes an ongoing process of neurogenesis, in which new neurons are continually generated throughout life. The axons of the sensory neurons leave the olfactory epithelium and transverse the skull base through the many openings of the cribriform plate to enter the olfactory bulb. Each olfactory sensory neuron expresses just one odorant receptor gene and these cells are distributed randomly within the olfactory epithelium [3]. Axons from the olfactory epithelium cluster in spherical structures in the superficial layer of the olfactory bulb, called glomeruli. The information passes to the mitral and tufted cells that provide the output to the higher olfactory centers. Numerous interneuron types exist in the olfactory bulb and modulate its activity. The accessory olfactory bulb, which resides on the dorsal-posterior region of the main olfactory bulb, forms a parallel pathway independent from the main olfactory bulb. It receives axonal input from the vomeronasal organ, which detects pheromones, among other chemical stimuli, and may influence aggressive and mating behavior.

THE PRIMARY AND SECONDARY OLFACTORY CORTEX

The olfactory tract carries the axons leaving the olfactory bulb to the structures collectively termed the primary olfactory cortex. The major constituents include the anterior olfactory nucleus, the olfactory tubercle and the piriform cortex. Projections of the piriform cortex, known to be the secondary olfactory areas, point to the amygdala, entorhinal cortex, orbitofrontal cortex and insular cortex. In order to reveal more detailed information regarding steps of odor processing, specific olfactory tasks are currently used in olfaction research (detection, discrimination, recognizing memory and identification) [4]. The piriform cortex appears to be involved in odor recognition memory [4]. Structures of the medial temporal lobe such as the hippocampus, perirhinal and parahippocampal regions are activated during odor discrimination, identification and memory (shown mainly in patients with temporal lobe epilepsy who had undergone medial temporal lobectomy). Electrophysiological stimulation within the temporal lobes shows that subjective smell experiences can be elicited by stimulation of the amygdala and uncus [5]. The amygdala is also involved in social functions such as mating. The orbitofrontal cortex is involved in perception of odor. The insula is a limbic-related cortex

and is activated by both olfactory and gustatory stimulation, especially when smell and taste are unpleasant. It also has an important role in the perception of pain and emotions such as anger, fear, disgust, happiness and sadness.

GENETICS

Familial studies have described olfactory deficits in asymptomatic first-degree relatives of patients with a neuropsychiatric disease including Alzheimer, Parkinson and schizophrenia [6]. Such findings suggest that olfactory functioning provides clues to the genetic imprinting of neuropsychiatry diseases or it can represent a biological marker for a comprised neural system. For example, relatives of schizophrenic patients were found to have altered thalamic and medial temporal lobe volumes. These abnormalities appear to be a subtler version of the changes observed in patients with schizophrenia and seem to be present to some extent from early childhood. In a study of olfaction in first-degree relatives of patients with schizophrenia, Moberg et al. [7] assessed the olfaction identification ability in 16 schizophrenics, 16 siblings and 32 controls. The schizophrenic patients revealed significantly reduced olfaction identification ability compared to controls and the siblings fell midway between them; among the siblings the scores were worse for those who met criteria for schizotypal personality disorder, and among the schizophrenic patients there was an association with illness duration. In twin studies, healthy monozygotic twins of patients with severe mental diseases had significantly worse olfaction identification ability than did twin pairs without such family histories [8]. The current data cannot explain why some relatives who show brain/olfactory pathology similar to that seen in patients with schizophrenia do not develop this illness. Further work needs to determine whether they have less severe pathology, whether the thalamus had been exposed to environmental triggers, or if they have protective factors. Nevertheless, some researchers advocate that olfactory deficits may serve as endophenotypes or as genetic vulnerability markers for neuropsychiatric disorders.

OLFACTORY NEURODEVELOPMENT AND PSYCHIATRIC DISEASE

A biopsy taken from inside the nose may be able to provide clues to neurological and psychiatric disorders. Freud, the father of psychoanalysis, believed that surgery on the nose could be an effective treatment for various psychiatric disorders. For example, we bring the hypothesis of schizophrenia which proposes that genetic and environmental factors alter early brain development to be at risk for developing this dis-

ease. Minor physical anomalies are noted in schizophrenia (subtle variations in the shape and proportions of the head, face, mouth, fingers, hands and dermatoglyphics) [9]. It has been suggested that key events altering proliferation, migration, differentiation and cell death during brain development may be related to these features [10]. MRI studies show these brains to be reduced in overall size, volume and weight compared to healthy controls. Other alterations include increased ventricular size and reduction in the volume of limbic structures such as the hippocampus, amygdala and olfactory bulb [11,12]. Olfaction in schizophrenia is impaired and the olfactory bulb is reported to be smaller. It may be speculated that neurogenesis may be impaired in the adult schizophrenic patient, specifically in the olfactory bulb, and this can contribute to olfactory dysfunction. Several studies have reported a greater proportion of immature and mature neurons as well as altered cell proliferation in olfactory epithelium from schizophrenic patients, indicating dysregulated neurogenesis in this tissue [13]. Some studies show that hormones, vitamins and growth factors could be regulators of olfactory neurogenesis. Other factors such as neural cell adhesion molecule and neurotransmitters might influence olfactory neurogenesis as well

Olfaction is a sense neglected by clinicians in routine work

[14]. It can be expected that a disease-induced neurotransmitter depletion or excess might impair neurogenesis. Medications used to treat psychosis and depression (e.g., olanzapine, risperidone, fluoxetine) have been shown to induce neurogenesis and to be neuroprotective in rats [15].

OLFACTION AND MEMORY

In *Remembrance of All Things Past*, Proust's description of dipping a cake into his tea and being completely transported by its aroma back to his childhood is one of the most frequently cited passages of literature. This is called the Proust phenomenon: a slightest hint of perfume can transform the present into the past, it can recreate entire sensory experiences by providing an emotional link between past events initially experienced through separate senses, and it can make memories seen real and tangible. Olfactory stimuli are more potent cues of autobiographical memories than other sensory stimuli. A clue to the olfactory-memory relation is the anatomical overlap between the structures involved in memory process and olfaction pathways. The orbitofrontal cortex is an area that receives sensory information that has already undergone processing. It receives gustatory, olfactory (through the piriform cortex) auditory and visual inputs, and integrates this information into unified perceptions [16]. For example, flavor is created from integrating information of taste and smell. The olfactory system is exclusive in that it has more direct contact with the external environment and

it directly projects into the brain via the olfactory bulb. The auditory and visual information reach the orbitofrontal cortex after having undergone significant processing including passage through the thalamus. Also, the cortical olfactory areas are phylogenetically older than other sensory cortical areas. This implies an anatomical and functional proximity to the limbic system that is much closer than other sensory modalities. Odor-cued memories are rated as more pleasant than memories cued via other modalities. The emotional potency of odor-evoked memory is correlated with specific activation in the amygdala. Odor cues to personal memories elicited greater activation in the amygdala-hippocampal complex than comparable, but non-personally relevant odors [17]. These data suggest that the amygdala-hippocampal complex may be part of the neural substrates involved in a distinct olfactory memory system.

SMELL AND DISGUST

The emotion of disgust appears to enable the avoidance of harmful substances. Like other emotions, it has characteristic facial expressions that can be recognized across cultures. Its purpose is to inhibit ingestion of a repulsive object: the nostril closing off serves to reduce input, whereas the opening mouth allows expulsion of offensive objects. There is evidence that the insula and basal ganglia have a role in experiencing disgust as well as identification of disgust in others. Recent studies show a connection between olfactory deficits and abnormal perception of disgust and the genesis of specific psychiatric disorders such as obsessive-compulsive disorder and phobias [18]. Brain regions most commonly associated with OCD in neuroimaging studies include the orbitofrontal cortex, the basal ganglia and insula [19]. Several studies compared the brain response to disgust stimuli in patients with OCD to that in healthy individuals. In one study increased insula activation was reported in response to disgust in both groups. However, when specific stimuli were employed, such as photographs of ashtrays or sinks, which evoke disgust only in OCD patients with contamination/washing symptoms, insula activation was reported only in patients with those symptoms but not in the control or OCD group with other symptoms. These results suggest that abnormalities in disgust processing may play a role for some OCD patients, especially those with washing rituals or contamination obsessions. Patients with OCD showed significant impairment in olfactory identification compared to healthy individuals, and most were classified as mild to moderately microsmic [20].

OCD = obsessive-compulsive disorder

SOCIAL FUNCTIONING

Social functioning is a key to survival and reproduction. For most mammals, social hierarchy and territory are recognized by odor, and smell plays a role in identifying enemies and determining safety from danger. During evolution, as humans developed language and other cognitive abilities, the selective pressure to maintain olfactory genes for survival and social function was reduced, and pseudogenes (loss-of-function mutations) accumulated in olfactory receptors. However, this does not preclude a key role for olfactory signaling in organizing the fetal brain or in developing social capacities. It was observed that humans who are congenitally blind, mute or deaf normally have intact reproductive-social behavior, but individuals with congenital anosmia usually do not [21]. There is a significant overlap in the neural circuitry that subserves olfaction and social function. The emotional processing of diverse stimuli rest on the phylogenetically older limbic circuits that evolved to process odors. Olfactory information projects to regions critical for mating, emotions and fear (amygdala and medial nucleus), and for motivation and high level cognitive and emotional process (orbital prefrontal cortex). Damaging these areas in lesion studies in primates resulted in increased aggression and loss of position in social hierarchies. In humans, accidental injury to the frontal cortex can lead to loss of normal social behavior and insight without intellectual loss. Schizophrenia can be used as an archetype for impaired social behavior in humans. As noted before, many cyto-architectural abnormalities in schizophrenia occur in olfactory areas. Smell identification deficits are trait-like abnormalities in schizophrenia. Up to 80% of patients with schizophrenia exhibit deficits in odor identification that are sufficient to interfere with daily functioning, whereas less than 15% of the general population show such deficits [22]. Impairments in social function and smell identification deficits could result from a common neurodevelopmental etiology.

SEX AND OLFACTORY FUNCTION

A modest female superiority has been demonstrated in virtually all olfactory functions measured. There is a widely held belief that women are differentially sensitive to odors during the course of the menstrual cycle. During ovulation women have been shown to prefer the scent of “symmetrical” men (males who are less likely to have experienced developmental aberrations). While this preference is present during ovulation, it disappears at other times during the menstrual cycle [23]. It has been observed that the reproductive performance of mice and humans can be influenced via urine odors. A preference

for major histocompatibility complex-dissimilar odor types has been reported in humans: in one study, the more attractive the odor the fewer HLA class I antigens that were shared. This suggests a potential mechanism for HLA-based odor recognition and perhaps mates' preferences in humans.

Le Magen (1952) proposed that gender differences should be more likely and prominent for biologically (sexually) relevant odors. Androstenedione, a testosterone derivative, is more likely to be detected by woman than men. It is also produced in boar testes and serves to induce lordosis (receptive posture) in the sow, and as such has been classified as a putative pheromone [24]. This compound has also been isolated in secretions from human axillae, more often in males than in females, and may serve similar purposes in humans. Moreover these odorants were rated as more pleasant around the time of ovulation than during the follicular and luteal phases of the menstrual cycle. This finding was not replicated in females using oral contraceptives. Woman who spend much of their time together (dormitories, cohabitating lesbians or woman who work together) have been documented to synchronize menstrual cycles [25]. Human female axillary secretions were shown to lengthen the ovarian cycle in recipient woman when collected from the ovulatory stage, and to shorten it when collected from the follicular stage. It is thought that pheromones mediate this effect by mediating the secretion of luteinizing hormone, luteinizing hormone-releasing hormone and follicle-stimulating hormone.

Examining the smell capability is easy and may have diagnostic and therapeutic potential

THE OLFACTORY SENSE AND ADDICTION

Current neurobiological models demonstrate dysfunction of the orbitofrontal cortex as a core underlying feature of addiction [26]. The brain's reward system consists of dopaminergic neurons projecting from the ventral tegmental area to the ventral striatum, amygdala, and prefrontal and cingulate cortices. This system mediates natural rewards (to food, water and sex) and appears to be a critical component of drug-induced reward. By inducing dopamine release, addictive drugs can become behavioral reinforcers. With chronic use, incremental neuroadaptations occur and render this system to be over-responsive (sensitized). These adaptations have been shown to persist long after detoxification, which may explain the substantial relapse rate among abstinent users. Recent neuroimaging studies demonstrated that frontal cortical regions (specifically the anterior cingulate cortex and OFC) are directly affected by long-term exposure to drugs of abuse. It has been proposed that dysfunction

within these brain regions is a key neural mechanism underlying addiction. However, it remains unclear whether it is a direct consequence of chronic use or reflects premorbid vulnerability. Neuroimaging studies showed decreased OFC volumes and activity correlated with olfactory dysfunction in patients with cocaine and alcohol dependence and increased activity within the OFC during drug intake and expectation [26]. Patients with OFC lesions or addiction showed impairment in decision-making tasks. Studies show a relationship between the tendency to act rashly and without consideration of consequences (called "rash spontaneous impulsivity") and substance use disorders. This behavior also inversely correlated with OFC volume and function in neuroimaging and with olfactory identification deficits. These data suggest that certain personalities may be associated with an increase vulnerability to addiction as a result of differential OFC functioning.

OLFACTORY IMPAIRMENT AND NEUROPSYCHIATRIC DISORDERS

Olfactory function decreases with age (50% exhibit major loss after age 65). Studies in Alzheimer's disease have identified impairments in olfaction, including identification and detection of odors. Typical histological Alzheimer changes are found in peripheral (anterior olfactory nucleus and olfactory bulb) as well as central olfactory areas [27]. Olfactory identification deficits may be an early feature of the disease and may help to discriminate it from multi-infarct or other dementias. The association between schizophrenia and olfactory dysfunction is well established. Abnormalities in brain development play a role in the pathophysiology of schizophrenia. A neurodevelopmental etiology is supported by findings of reduced cranial size and minor midline physical anomalies. These anomalies arise from the same embryonic process that produces olfactory structures. Abnormalities in neuron size, orientation and packing density in limbic and associated cortices have been described as well. The examination of peripheral parts of the olfactory system revealed that the volumes of olfactory bulbs of schizophrenic patients were statistically smaller than of healthy controls. Healthy family members had volume reductions only for the right olfactory bulb. Several studies evaluated metabolic activity in olfactory-related regions using functional imaging. All of the schizophrenic patients had lower rates of frontal metabolism; however, 50% of them were also microsmic (by assessment of University of Pennsylvania Smell Identification Test score). Olfactory deficits have been demonstrated also in Huntington's disease. Olfactory dysfunction may be a reliable early marker of Huntington's disease after illness onset.

OFC = orbitofrontal cortex

Deficits in olfactory threshold and identification ability in human immunodeficiency virus-infected persons have been consistently reported. Mild impairment in olfactory function might be an early indicator of immune suppression or of neurological disease. Neuropathological studies identified HIV receptor clusters in olfactory tracts and bulbs as well as limbic system [28], but other studies could not exclude the contribution of peripheral nerve damage and other effects related to treatments, such as AZT (azidothymidine). Olfactory deficits are not a prominent feature of depression, and conflicting evidence is reported. While the evidence for olfactory identification deficits in depression and obsessive-compulsive disorder is not strong, it is a common clinical observation that people who are depressed often report a lowered ability to enjoy odors. Right hemispheric OFC deficits have been reported in many studies with attention deficit hyperactivity disorder.

OLFACTION AND PARKINSON

In recent years, focus on the olfactory function of extrapyramidal disorders has increased with the recognition that patients with idiopathic Parkinson's disease are hyposmic [29]. It remains possible that the olfactory system is the site of initial damage in IPD and that the motor component is a late manifestation of what is a primary olfactory disorder. This may afford the possibility of neuroprotective therapy. Patients and clinicians are usually unaware of hyposmia and some complain of loss of taste instead. When anosmia is intermittent, the cause is probably conductive; continual anosmia is usually a sign of a sensorineural loss. In one study, the olfactory neuroepithelium in patients with IPD was found to have dystrophic neuritis. Olfactory bulbs and tracts from brains with clinical IPD showed cortical type lewy bodies in the anterior olfactory nucleus, but they were also found in mitral cells [30]. In another study, most patients with IPD showed a decreased olfactory evoked response, which correlated with University of Pennsylvania Smell Identification Test (UPSIT) measurements. Other studies demonstrated that some first-degree relatives of patients with IPD demonstrate abnormal olfactory identification ability, suggesting that the UPSIT may be an early detection tool for the asymptomatic state of IPD. The olfactory system is damaged in other parkinsonian syndromes as well: namely, severe damage in Guamanian and lewy body disease, intermediate involvement in multiple system atrophy and drug-induced parkinsonism and least involvement in vascular parkinsonism and progressive supranuclear palsy [31]. These differences can aid in the diagnosis.

HIV = human immunodeficiency virus
IPD = idiopathic Parkinson's disease

OLFACTION AND AUTOIMMUNITY

The immune and olfactory systems are both influenced by external stimuli of our close environment. Smell perception in each individual is affected by the combination of genetic, hormonal and environmental factors, similar to the mosaic that encompasses autoimmunity [32].

Many interactions exist between the immune and olfactory systems. In insects for example, the immune system of bees was modified by lipopolysaccharide and this reduced their ability to associate odor with sugar [33]. Studies have shown that odorants may suppress immune reaction in mice. Inhaled odorants were shown to protect mast cell activation by blocking the induction of substance P or the stress-induced activation of suppressor T lymphocytes. It has been demonstrated that when immunological function is impaired (such as in autoimmunity), olfaction can be affected and vice versa. For example, olfactory bulbectomy, used commonly as a model of depression in rodents [34], leads to an impairment in immunological function and blunts the immune response to LPS [35]. Olfactory abnormalities may be associated with various autoimmune conditions. Olfactory function is damaged in multiple sclerosis, a well-established autoimmune-central nervous system disease. Patients with this disease

have low UPSIT scores, which correlate with the severity of their neurological impairment [36]. Smell deficiency

in these patients was associated with anxiety and depression. Patients with systemic lupus erythematosus, a multi-organ autoimmune disease, have various degrees of CNS involvement. CNS-SLE is associated with more than 20 different autoantibodies, particularly the anti-P-ribosomal antibodies, which induce depressed-like behavior in mice. In our previous studies [37] we demonstrated that these antibodies attach to limbic and olfactory (piriform and cingulate cortex) areas. It has been shown that other antibodies could alter emotional behavior in rodents with a SLE-model as well. Recent studies showed that patients with SLE had significant hippocampal atrophy that correlated with disease duration, total corticosteroid dose and greater number of CNS manifestations [38]. The hippocampus, located in the temporal lobe, is a structure intimately associated with olfaction. In another study, patients with neuropsychiatric SLE were found to demonstrate selective damage to the amygdala compared to healthy controls [39]. Among these patients, some had anti-DNA antibodies that cross-react with NMDA receptors, accompanied by more severe damage to the amygdala [40]. This latter finding may connect autoantibodies to limbic/olfactory region insults and

LPS = lipopolysaccharide
CNS = central nervous system
SLE = systemic lupus erythematosus

may help to elude the connection between autoimmunity, depression and smell.

SUMMARY

Although our knowledge of the brain, the olfactory sense and autoimmunity continues to evolve, examining the olfaction ability is not yet routinely applied by clinicians in the process of diagnosis and treatment. Moreover, assessment of the sense of smell and olfactory impairments is usually overlooked by patients and their clinicians. Given the clinical data reviewed here, clinicians should be encouraged to screen for olfactory impairments, which can help in the early diagnosis of CNS diseases such as Parkinson, dementia and schizophrenia, as well as CNS-autoimmune diseases such as neuropsychiatric lupus.

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