Neuroimaging in Patients with Olfactory Dysfunction

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This review summarizes neuroimaging findings in patients with olfactory dysfunction. Neuroimaging techniques offer a valuable means for evaluating and distinguishing disorders of olfaction. The new or refined techniques make it possible to pinpoint the anatomic and pathologic changes of many disorders of the sinonasal cavity and brain that cause olfactory deficits. From an anatomic point of view, the causes of olfactory deficits generally can be classified as peripheral or central (intracranial). In the assessment of the peripheral causes, CT and MR imaging reveal anatomic information and structural changes, enable a differential diagnosis, and provide a road map for surgical intervention. In the evaluation of the central causes, MR imaging, positron emission tomography, or single-photon emission computed tomography can provide the links between olfactory dysfunction and structural or functional changes in the brain.

Olfactory dysfunction generally is classified as either a peripheral conductive disorder caused by interference with the access of odors to the olfactory receptors in the sinonasal tract or as a central sensorineural disorder resulting from injury to the olfactory receptors (within the olfactory mucosa); the olfactory bulb or tract; or related parts of the CNS such as the prefrontal lobe, septal nuclei, amygdala, and temporal lobe [1]. Although revolutionary changes in medical imaging techniques have occurred in the past few decades, few articles have dealt with imaging studies in patients with chemosensory disorders [2–6]. We reviewed the publications on this topic in an effort to bridge the chasm between imaging and clinical assessment of patients with olfactory deficits.

Basic Anatomy and Physiology of the Olfactory System

The sensation of smell is induced by the stimulation of olfactory receptor cells by volatile chemicals. The olfactory receptor cells—that is, the primary olfactory neurons—are encompassed in the neuroepithelium located at the top of the nasal vault, the upper portion of the nasal septum, the superior surface of the superior nasal turbinate, and the region of the cribriform plate. Afferent information from the receptors is transmitted by the olfactory nerves, which course through the cribriform plate of the ethmoid bone to terminate in the glomeruli of the olfactory bulb [7]. From there, the efferent neurons of the olfactory bulb give rise to fibers that form the olfactory tracts, which lie just under the gyrus rectus region in the olfactory sulcus of the frontal lobes. Axons project to central limbic system components, including the piriform cortex and adjacent corticomedial amygdala (which together form the uncus), the ventral striatum, the parahippocampus, and the anterior olfactory nuclei. From these areas there are widespread interconnections with many parts of the brain, including the dorsal medial thalamus, hypothalamus, orbitofrontal and dorsolateral regions of the frontal cortex, temporal cortex, and other areas of the limbic system [7, 8].

Imaging Techniques

Major advances in pinpointing the anatomic and pathologic changes of many disorders of the sinonasal cavity and brain have become possible because of recent developments and refinements in imaging techniques [9–16]. Although the imaging evaluation is not the diagnostic equivalent of a histologic study, an anatomic imaging technique such as high-resolution CT and MR imaging can not only map regional lesions but also may enable a differential diagnosis [9, 10, 13, 14]. Functional imaging, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT),...
affords the potential for exploring regional pathophysiologic changes in the living brain [12, 15, 16].

Because of their low sensitivity, low specificity, and inability to show the ostiomeatal complex, plain radiographs play only a minor role in the imaging evaluation of olfactory dysfunction.

CT is well suited to the study of the sinonasal cavities. Because CT is as sensitive to soft-tissue disease as to bony changes, each scan can be photographed at an appropriate window width and level to optimally show insidious soft-tissue differences in attenuation and fine bony detail. The basic CT scanning protocol should include all of the nasal cavity, paranasal sinuses, hard plate, anterior skull base, orbits, and nasopharynx. The brain should be included if central causes of olfactory dysfunction are suspected. Thin-section scans are commonly obtained in both the axial and coronal planes for optimal assessment of the complex paranasal anatomy, but coronal scans are the most valuable for the anterior nasoethmoidal (ostiomeatal complex) region (Fig. 1). IV contrast enhancement is usually reserved for identification of vascular lesions, tumors, meningeal or parameningeal processes, and abscess cavities [10].

The multiplanar capability of MR imaging is especially advantageous in the evaluation of sinonasal tract neoplasms and brain disorders. MR imaging, however, is less sensitive for the detection of bony cortical abnormalities and landmarks. Soft-tissue discrimination is more clearly illustrated with MR imaging than with CT. Most soft-tissue diseases can be accurately localized with a degree of tissue differentiation, that is, infection vs tumor vs hemorrhage. T2-weighted and enhanced MR images can better delineate the contrast between normal and inflammatory (rim-enhancing) or neoplastic (solidly enhancing) tissue [11, 14]. MR imaging is the study of choice to evaluate the olfactory bulbs, olfactory tracts, and intracranial causes of olfactory dysfunction [4, 6].

In general, scintigraphy plays no significant role in the diagnostic workup of patients with suspected sinonasal tract disease, except in the case of CSF leaks. Functional imaging studies, such as PET and SPECT, are valuable in detecting alterations of regional brain function and biochemistry in vivo [15–18].

**Peripheral Causes of Olfactory Disturbance**

Sinonasal tract disease is one of the common causes of olfactory disturbance [5]. The cause of olfactory deficits among patients with nasal and paranasal sinus disease is most likely nasal airway obstruction. Any cause of bilateral obstruction can decrease smell sensations by limiting air flow to the olfactory receptors [19]. Besides the obstructive effect, lesions in the upper nasal vault and/or cribiform plate region can also directly damage the olfactory epithelium and olfactory neurons. The common peripheral sinonasal tract causes of olfactory deficits include infections, tumors, allergic rhinosinusitis, and congenital or developmental abnormalities.

**Sinonasal Infectious Disease**

Although the exact cause of chemosensory dysfunction due to sinusitis is elusive, alterations in nasal air flow and mucociliary clearance or obstruction from secretory products, polyps, or retention cysts may contribute to olfactory dysfunction [20].

At present, high-resolution CT is the preferred imaging technique, preceded by endoscopic nasal examination. Air-fluid levels are usually indicative of acute sinusitis, whereas mucoperiosteal thickening can be seen in acute and chronic disease. CT is an excellent imaging technique for the evaluation of bony abnormalities, such as osteitis or remodeling seen in some inflammatory lesions. CT will help the functional endoscopic sinus surgeon in planning effective surgery to restore normal mucociliary clearance. MR imaging also is highly sensitive for detecting mucosal thickening and other soft-tissue abnormalities [9]. By and large, inflamed mucosa is usually high in signal intensity on T2-weighted MR images and low in intensity on T1-weighted images. Secondary formation of polyposis, retention cysts, or mucocelle of sinonasal cavities can be clearly detected with either CT or MR [9, 21, 22] (Fig. 2).

![Fig. 1.—Normal ostiomeatal complex. Coronal bone-targeted CT scan shows maxillary sinus ostium (a) and infundibulum (open arrow) between uncinate processes (solid arrow) and ethmoidal bulla (b). Air channel (arrowhead) medial to uncinate process is middle meatus. t = middle turbinate.](image1)

![Fig. 2.—Sinonasal polyposis in a 43-year-old man with a history of decreasing smell sensation and nasal obstruction. Coronal CT scan shows nearly complete opacification of sinonasal cavity bilaterally. Expansion of maxillary sinus ostium (solid arrow) and erosion of ethmoidal labyrinth (e) and uncinate processes (open arrows) are caused by polyps.](image2)
NEUROIMAGING IN OLFACTORY DYSFUNCTION

Tumors of the Nasal Cavity and Paranasal Sinuses

Almost all sinonasal tract tumors and tumorlike entities that grow to a large size can cause a decline in olfactory acuity by interfering with patency of the nasal airway or by directly destroying the olfactory receptors. A classic example of an intrinsic sinonasal tract tumor, an olfactory neuroblastoma, often causes hyposmia or anosmia and may serve as the prototype for masses in this region.

Olfactory neuroblastoma, or esthesioneuroblastoma, is a nasal tumor originating from the olfactory neuroepithelium lining the roof of the nasal vault and in close proximity to the cribiform plate. In the detection and staging of olfactory neuroblastoma, CT and MR imaging are essential. Generally speaking, MR imaging is more accurate than CT in showing the tumor's intracranial extent (Fig. 3A). MR imaging also is useful for differentiating neoplasm from postobstruction secretions because of differences in signal intensity (most secretions are bright on T2-weighted images, whereas tumor has intermediate signal intensity) and contrast enhancement (tumor enhances solidly, secretions show rim mucosal enhancement). Unfortunately, the signal intensity characteristics of various sinonasal tract tumors overlap, so MR imaging often cannot be used to predict specific tumor histology [13, 23]. Other sinonasal tract tumors, such as inverted papilloma, squamous cell carcinoma (Fig. 3B), adenocarcinoma, and melanoma, also can cause hyposmia or anosmia during their late stage.

Allergic Rhinitis

Allergic rhinitis is a common condition in the upper airway that affects about 30 million Americans, with peak prevalence in persons 35–54 years old. Hyposmia or anosmia is common with allergic rhinitis, which is caused mainly by nasal obstruction by polyps or inflamed mucosa that limits access of inspired air to the roof of the nasal vault [24]. CT and MR imaging are important for detecting any complications such as sinusitis, mucoceles, and aggressive polyps in patients with allergic rhinitis. Rounded excrences and enlargement of ostia are seen in the airway of patients with polyposis.

Congenital or Developmental Abnormalities

Congenital and developmental abnormalities include choanal atresia, hereditary nasal septal deviation, facial hypoplasia, cleft palate, nasal dermoids, epidermoids, cephaloceles, and gliomas. Medical imaging techniques, especially high-resolution CT, play a key role in detecting and evaluating the facial and bony changes [25, 26], because surgical correction requires identification and closure of the osseous abnormalities. MR imaging is most effective in defining soft-tissue or CSF-containing masses such as cephaloceles and nasal gliomas.

Others

Thirty million Americans have used cocaine, and 5 million use it regularly [27]. Although hyposmia or anosmia has been suggested to occur often in cocaine abusers, few studies using quantitative measures of olfactory function have confirmed such reports. The mechanism of olfactory disturbance with heavy cocaine use is still unclear. Conceivably, the disturbance could be due to conductive disorders, nasal airway obstruction, alteration in sinonasal aerodynamics, damage to olfactory epithelium, osteolysis of the cribiform plate, or damage to the central olfactory system. Several CT reports of osteolytic sinusitis and extensive osteocartilaginous necrosis of the nasal septum due to cocaine abuse have been published recently [28–30].

Vasculitic infarcts, hypertensive hemorrhages, and white matter ischemic foci can be seen in cocaine users. Tumeth et al. [31] showed multifocal cortical deficits with a special predilection for the frontal and temporal lobes on SPECT perfusion brain scans in chronic cocaine abusers.

Olfactory deficits can also accompany Wegener’s granulomatosis, Paget’s disease, fibrous dysplasia, and leprosy [32]. The mechanism of the olfactory deficits from these diseases is most likely related to conductive disorders of the sinonasal tract due to bony or soft-tissue destruction of the airway.

Central Causes of Olfactory Disturbance

Numerous CNS disorders may be associated with olfactory dysfunction. The most common types fall into the categories of degenerative neuropsychiatric disorders, hereditary conditions, trauma, and neoplasms.

Alzheimer’s Disease

It is well documented that olfaction is significantly altered in persons with Alzheimer’s disease. Nearly all studies of olfactory function in patients with Alzheimer’s disease have reported decreased smell relative to that of age-matched control subjects. These studies show marked impairment of smell identification and an increased threshold for odor detection in early Alzheimer’s disease [33–35].

The anterior olfactory nuclei, olfactory bulbs, and central olfactory structures (amygdala, temporal lobes) in patients with Alzheimer’s disease show senile plaques, neurofibrillar tangles, granulovascular degeneration, and cell loss [36, 37]. Early CT studies in patients with Alzheimer’s disease showed generalized enlargement of the ventricular system and sulci [38]. Several reports have noted that ventricular and sulcal enlargement correlate well with the severity of the disease [39]. De Leon et al. [40] have emphasized the rate of change in ventricular size with CT scans obtained over time as an important index in the diagnosis of this disease. Recently, several investigators have recognized that CT or MR imaging delineation of atrophic changes in the temporal lobe and the hippocampus with enlargement of hippocampal-choroidal fissures strongly supports the diagnosis of Alzheimer’s disease [41–43] (Fig. 4).
The major findings of functional imaging studies in patients with Alzheimer’s disease are abnormal regional blood flow pattern and flow reduction in the cerebrum. The common sites of blood flow reduction are in the temporoparietal region and the frontal areas. In a recent report [44], only frontal flow abnormalities were seen on SPECT scans of seven patients with a possible diagnosis of Alzheimer’s disease. Is this an early imaging finding that may suggest a pathophysiologic basis to explain the decreased smell sensation in patients with Alzheimer’s disease?

**Parkinson’s Disease**

Odor detection and identification are significantly impaired in patients with Parkinson’s disease [45]. Research into the cause of smell dysfunction in patients with Parkinson’s disease has focused on dopaminergic changes. Patients with Parkinson’s disease show significantly reduced blood flow of °F-dopa in the caudate nuclei and putamen, a reduction of striatal dopamine storage, and reduced activity in basal ganglia [17]. However, the olfactory deficit is unrelated to severity of motor or cognitive symptoms, and is not improved by L-dopa therapy [46].

The major feature of Parkinson’s disease on MR imaging appears to be a trend toward a decreased width of the pars compacta of the substantia nigra [47]. T2-weighted MR images occasionally show abnormal decreased signal intensity in the putamen and to a lesser degree in the caudate nuclei and substantia nigra, suggestive of iron deposition [48]. PET and SPECT studies in patients with Parkinson’s disease show a moderate global decrease in the cerebral metabolism, especially in the temporoparietal region (Fig. 5).

**Huntington’s Disease**

Patients with Huntington’s disease may have olfactory dysfunction [35]. Theoretically, the input of fibers from the caudate and putamen to the limbic system and striatum may be altered, leading to olfactory dysfunction, but the exact mechanism for hyposmia in patients with Huntington’s disease has not been established. On CT scans and MR images, a decrease in the volume of the caudate head and an increase in the intercaudate distance are seen [49, 50]. PET scans of patients with Huntington’s disease have consistently shown decreased metabolism in the caudate nuclei, often before the development of atrophy is shown by CT [17]. SPECT studies involving patients with Huntington’s disease have also revealed decreased uptake of °I-isopropyl iodocamphetamine in the caudate nuclei.

**Korsakoff’s Psychosis**

Patients with Korsakoff’s psychosis exhibit impaired odor detection, identification, and intensity estimation [51]. Olfactory perception may be selectively impaired in patients with Korsakoff’s psychosis by the diencephalic lesions that are characteristic of this disease. Degeneration of the dorsal medial thalamic nucleus (the common neuropathologic lesion seen in Korsakoff’s psychosis) and atrophy in the prefrontal areas also can cause the olfactory dysfunction.

Patients with Korsakoff’s psychosis show widespread volume reductions in gray matter, diencephalic structures, mesial temporal lobe structures, and orbitofrontal cortices (areas involved in olfaction perception). Reversible diencephalic (medial thalamic) and mesencephalic (periaqueductal) lesions can be seen on T2-weighted MR images [52].
Schizophrenia

Impaired olfactory function has been reported in schizophrenic patients, especially males [53, 54]. These olfactory deficits, which are not of the same magnitude as those seen in Alzheimer's disease and Parkinson's disease, are perhaps not unexpected, given the occurrence of olfactory hallucinations as symptoms in a number of patients with schizophrenia and the evidence linking both to temporal lobe dysfunction [55, 56]. Functional imaging has provided some evidence that certain schizophrenic patients have decreased blood flow and metabolism in the frontal lobes (hypofrontality) [17] (Fig. 6).

The most consistent finding, on both CT scans and MR images, is enlargement of the cerebral ventricular system, especially in the frontal and temporal horns, and corresponding decreases in cerebral tissue [57, 58]. One study [57] found that the volume of gray matter in the temporal lobe was 20% less in patients than in control subjects, and lateral ventricular volume was 67% larger in the schizophrenia group than in the control group.

Congenital Anosmia

Congenital anosmia, which traditionally has been defined as anosmia present from a patient's earliest recollection, has been recognized for centuries. The most common form of congenital anosmia is Kallmann's syndrome or olfactory dysplasia, which is characterized by hypogonadotropic hypogonadism and anosmia [59]. Pathologic and surgical studies of patients with Kallmann's syndrome have shown agenesis of the olfactory bulbs [60, 61].
Surface-coil MR imaging is the optimal technique for revealing the intricate details of the olfactory bulbs, olfactory tracts, and rhinencephalon in vivo (Fig. 7). Three recently published studies of the imaging findings in Kallmann's syndrome have reported these findings: (1) absence of olfactory bulbs and tracts, (2) hypoplasia of olfactory bulbs and tracts, and/or (3) absence or hypoplasia of olfactory sulci [6, 62, 63] (Fig. 8). The volumes of the pituitary gland, hypothalamus, and frontal and temporal lobes were characteristically normal.

**Head Trauma**

Craniofacial trauma can alter olfactory ability through one of several mechanisms: damage to the nose, sinuses, or both with resultant mechanical obstruction to odorants; shearing of olfactory filaments as they course through the cribriform plate; contusion of the olfactory bulb; and contusion or shearing injury of the cerebral cortex, particularly the frontal and temporal lobes [32, 64]. The prevalence of anosmia or hyposmia after head trauma has been reported quite variably from 2% to 38% [65-69], and the prevalence increases with the severity of injury [66]. Evidence has shown that frontal or temporal lobe hematomas or contusions are one of the most common causes of olfactory dysfunction after head injury (Fig. 9).

CT currently is the study of choice when diagnostic imaging is necessary after acute head trauma [70, 71]. CT can show subarachnoid hemorrhage, fractures, and intraventricular blood, lesions for which MR imaging is less sensitive acutely. However, MR imaging is superior to CT for detecting and characterizing subacute injuries, hemorrhage outside the subarachnoid space as in subdural hematomas, cortical contusion, and shearing injuries. MR imaging is exquisitely sensitive to diffuse axonal injuries leading to demyelination. In the lower frontal regions and near the olfactory bulbs, bone artifacts will inhibit the ability of CT to determine the cause of posttraumatic hyposmia. MR imaging may be required.

**Brain Tumor**

The prevalence of chemosensory changes caused by intracranial tumors has rarely been investigated. In a recent study of 750 consecutive patients with chemosensory disorders seen at the University of Pennsylvania Smell and Taste Center, only two cases (0.3%) were induced by brain tumors [65].

In general, tumors or other destructive lesions involving the olfactory bulb, olfactory tract, or prefrontal lobe can cause olfactory deficits [72, 73]. Temporal lobe tumors usually cause olfactory hallucinations (Fig. 10). The presence of olfactory deficits correlates more with the location of tumors than with the histologic findings.

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**Fig. 7.**—Normal olfactory bulbs in a 64-year-old healthy female volunteer with normal smell function. Coronal surface-coil MR image (500/20 [TR/TE]) shows normal olfactory bulbs (arrows).

**Fig. 8.**—29-year-old man with Kallmann’s syndrome. Coronal MR image (500/20 [TR/TE]) shows bilateral absence of olfactory bulbs and tracts, a flattened gyrus rectus (arrow) on right side, and a normal-appearing gyrus rectus on left side.

**Fig. 9.**—20-year-old woman with posttraumatic anosmia. Coronal T2-weighted MR image shows encephalomalacia. Hyperintense signal (S) has replaced inferior part of frontal lobes (where smell processing occurs).

**Fig. 10.**—Glioblastoma multiforme in temporal lobe of a 62-year-old woman with olfactory hallucinations. Contrast-enhanced T1-weighted MR image shows moderate enhancement of mass in temporal lobe and a satellite nodule (n) laterally. Sulci are effaced and temporal horn is obliterated.
Impaired olfaction might serve as a marker of early involvement of the CNS in HIV-infected patients [74]. Everall et al. [75] found that the numeric density of neurons in the frontal cortex was significantly lower in a group with HIV than in a control group; patients with AIDS had about 38% fewer neurons in the superior frontal gyrus. This may account for the olfactory deficits in these patients. Patients with HIV infection have widened cortical sulci, enlarged ventricles, and cerebral and brainstem atrophy when compared with control subjects [76–78]. Opportunistic infections and CNS lymphoma may be superimposed on these changes. In addition to CNS changes, sinusitis in HIV-infected patients is common and severe. The possibility of a peripheral cause of olfactory deficits in patients with AIDS also has to be considered in certain cases.

Others

There are also reports of olfactory dysfunction with major depression, hypochondriasis, and multiple sclerosis [32]. Although the pathogenesis of olfactory dysfunction in these disorders is still unclear, it appears that a central mechanism rather than a peripheral one is operational.

Discussion

Loss of smell sensation is a common finding associated with many diseases. It has been estimated by the National Institutes of Health that more than 2 million people in the United States have a smell dysfunction [32]. The investigation of smell loss has long been neglected because the lack of olfaction has seldom been considered a major disability, and easy-to-use quantitative tests of olfactory function applicable to clinical assessment have not been generally available. However, olfactory deficits can produce significant impairment in the quality of life. Once an olfactory disorder has been recognized, the most important step in the diagnostic process is to determine the site of the lesion. Unfortunately, current clinical olfactory testing is unable to localize the morphologic changes [79]. Modern imaging techniques can be of great value in the anatomic classification and localization of the common causes of olfactory dysfunction. The most common source of olfactory dysfunction is the peripheral pathway [32]. At present, high-resolution CT, especially coronal scanning, is the technique of choice for studying the bony sinusonal structures and the osteomeatal complex. CT can also provide important information as a road map for surgical treatment.

MR imaging is especially useful in soft-tissue discrimination and offers multiplanar capabilities. In the evaluation of the central causes of olfactory disturbances, MR imaging has a paramount role. Neuroimaging studies of patients in the neuropsychiatric group with olfactory deficits have revealed interesting findings: the links between olfactory deficits and pathophysiologic changes in the brain. The neuroimaging findings in patients with Alzheimer’s disease, Korsakoff’s psychosis, or schizophrenia have some similarities. Almost all of the abnormalities of the brain parenchyma revealed by radiologic studies in patients with these diseases have involved the areas that are the central olfactory projections, such as the prefrontal lobe, temporal lobe, hippocampus, and thalamus.

In the group with congenital disease, such as Kallmann’s syndrome, the cause of anosmia can be seen on MR studies as absence or hypoplasia of the olfactory bulbs [6]. Other congenital abnormalities such as choanal atresia and meningoencephalocoeles also can be detected with the imaging studies. In the categories of head trauma and brain tumors, imaging studies have shown strong links between olfactory dysfunction and the location of the damaged brain. The histology of the tumor or traumatic injury is less critical than its location [2, 64, 72].

Hyposmia or anosmia induced by occupational, recreational (cocaine), or accidental exposure to toxins also has been thought to be due to damage to the peripheral pathways. However, one study has suggested that olfactory deficits caused by occupational exposure to toxins may have both peripheral toxic and CNS effects [80].

Conclusions

Medical imaging is an essential part of the evaluation of olfactory disorders. In the assessment of peripheral causes of olfactory deficits, CT and/or MR imaging will reveal anatomic information and structural changes, enable a differential diagnosis, and provide a road map that may be needed for surgical intervention. In the evaluation of central causes, MR imaging, PET, or SPECT can provide the links between olfactory dysfunction and the structural or functional changes in the living brain.

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REFERENCES

2. Schelling D, Henkin RT, Smirnopolous JG. CT of the brain in taste and smell dysfunction. AJNR 1983;4:752–754
12. Healy B. From form to function: better imaging techniques extend study of living system (from NIH). JAMA 1992;267:286
17. Alavi A, Hirsch LJ. Studies of central nervous system disorders with single photon emission computed tomography and positron emission tomogra-