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Olfactory dysfunction: testing in neurological disorders

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Introduction

The relationship of the olfactory pathways to the limbic system and behavior has led to a resurgence of clinical research in olfaction. Since the second and third order olfactory neurons project directly into limbic structures involved in memory and learning, the study of olfaction may expand our understanding of cognitive disorders.

Olfactory testing

There is no universally accepted method of olfactory testing, largely because there is no generally accepted odor classification scheme. However, several tests of olfaction have been developed for clinical use. Some of these tests use dilutions of several odorants with which odor detection and/or odor identification thresholds are subjectively determined [1,2]. The Smell Identification Test (Doty *et al.*, *Physiol Behav* 1984, 32:489-502), a multiple choice 'scratch and sniff' test of 40 odorants, provides a reliable estimate of olfactory function without the necessity of mixing odorants and diluents. This test correlates with odor threshold determinations but, as with any odor identification test, relies quite heavily on preserved language ability.

A more sophisticated method of olfactory testing involves the use of 'olfactometers' which introduce air streams or bursts of odorant-saturated air into the patient's nose. These are the most accurate systems for determining threshold because the amount of odorant delivered can be more precisely controlled. Unfortunately, olfactometers are complicated and suffer from technical problems such as odor contamination, differences in flow rate and

pressure, and interference with normal breathing (and smelling) patterns. Further research with olfactometers is necessary to establish standards for odorant stimulus parameters such as flow rate and duration.

The National Geographic Smell Survey [3] was recently conducted in co-operation with the Monell Chemical Senses Center in Philadelphia. One and a half million readers of this magazine responded to a questionnaire in the September 1986 issue containing 6 'scratch and sniff' panels. The questionnaire asked participants to identify the samples to rate their 'strength' and 'pleasantness'. Responses were correlated with demographic data obtained in the questionnaire. Preliminary analysis of 126 000 responses has confirmed previous reports of gender differences in olfaction and a decline in olfactory sensitivity with age that accelerates around the eighth decade. As the data are thoroughly analyzed over the next few years, information about geographic and work-related differences in olfactory sensation may provide clues to clinical problems in olfaction. Readers wanting more information about olfactory physiology and testing can peruse *The Neurobiology of Taste and Smell* edited by Finger and Silver (John Wiley and Sons, 1987). The current clinical status of olfaction is described in the review of smell and taste disorders by Estrem and Renner [4].

Olfaction and dementia

Diseases of the limbic system such as dementia of the Alzheimer type (DAT) (Warner *et al.*, *Biol Psychiatr* 1986, 21:116-118), Korsakoff's psychosis (Mair *et al.*, *Neurophysiologia* 1986, 24:831-839)

and temporal lobe epilepsy (Eskenazi *et al.*, *Neuropsychologia* 1986, 24:553–562) can be accompanied by olfactory deficits. These deficits may develop because of the close connections between the olfactory cortex and limbic structures such as the hippocampus, the dorsal medial nucleus of the thalamus and the amygdala. Both odor identification and odor detection deficits have been described in DAT [5]. A correlation has recently been reported between n-butanol detection thresholds and scores on the Blessed Dementia Rating Scale, the Mini-Mental State Exam and the Dementia Rating Scale in patients with DAT, implying a relationship between the two processes (Jensen and Murphy. Olfactory thresholds in Alzheimer's disease are correlated with neurophysiological assessment of dementia. *In* Association for Chemoreception Sciences, Tenth Annual Meeting, 1988, abstract 127).

Does the olfactory system allow some infectious or toxic agent access to the limbic system in DAT? The primary olfactory sensory neurons are exposed directly to the external environment and actively transport chemicals such as horseradish peroxidase [6] into the brain as well as providing a portal of entry for some viruses [7,8]. However, the recent finding in DAT that neurofibrillary tangles are present in tufted cells and granule cells of the olfactory bulb, but absent in mitral cells [9], tends to argue against an olfactory 'portal' hypothesis. The mitral cells receive most of the afferent projections of olfactory nerve and comprise the primary sensory input to anterior olfactory nucleus and piriform cortex. Thus, a significant reaction would be expected in these cells if they were transporting a pathogenic agent responsible for Alzheimer's disease. Theories regarding inhaled aluminosilicates as a cause of DAT have been refuted by the finding of normal intracellular aluminum concentrations by X-ray microanalysis in tangle-bearing neurons of a patient with DAT [10]. In as much as Down's syndrome may be used as a model of DAT, the appearance of tangles in the entorhinal cortex and hippocampus before their appearance in the olfactory bulb and piriform cortex in these patients also argues against an olfactory origin for DAT (Mann *et al.*, *Neuropathol Appl Neurobiol* 1986, 12:447–457). Interestingly, odor identification deficits have recently been described in Down's syndrome [11].

Moberg *et al.* [12] have suggested that olfactory recognition tasks are more affected by subcortical pathology than are verbal and visual memory tasks. These investigators found severe impairment of olfactory memory with relatively normal visual and verbal recognition and normal olfactory discrimi-

nation in patients in the early stages of Huntington's disease. In comparison, patients with early DAT and comparable Mini-Mental State Exam scores exhibited significant deficits in all three modalities. Olfactory deficits have also been reported in patients with Parkinson's disease on both levodopa and/or anticholinergics [13].

Unfortunately, the diagnostic utility of existing tests of olfactory function is limited in the elderly population because of normal age-related losses in olfactory sensitivity. Kesslak *et al.* [14] have found an impairment in the ability of DAT patients to discriminate novel odors as compared to more familiar odors using a match-to-sample paradigm. Perhaps, by careful selection of odorants, specific deficits associated with specific diseases can be found. Such tests might differentiate between olfactory deficits due to age, intranasal pathology or neurological disease and prove useful diagnostically. For instance, the absence of odor identification deficits in patients with major depressive disorders [15] may be useful in differentiating dementia and the 'pseudo-dementia' of depression

Olfaction and evoked potentials

Evoked potentials are an objective and quantitative measure of sensation and might allow differentiation of pathologic processes producing olfactory deficits. Olfactory evoked potentials elicited by a 250 ms stimulus of amylacetate have been recorded from the brain and skull of rats with transected vomeronasal and ciliary nerves (Inokuchi *et al.*, *Laryngoscope* 1986, 96:1107–1111). The response consisted of a broad, negative-positive-negative waveform over the frontal cortex and coronal suture with latencies of 110, 250 and 550 ms respectively (including a transit time of the odorant from the nares to the olfactory epithelium). The waveform totally disappeared after ablation of the olfactory bulb and was altered by removal of the prepiriform cortex. These data suggest that evoked potentials recorded from the skull in response to odorants can reflect electrophysiologic processes underlying olfaction in the bulb and olfactory cortex.

Plattig and Kobal (*In* Human Evoked Potentials: Application and Problems edited by Lehmann and Callaway. Plenum Press, 1979, pp 285–301) reported a negative-positive-negative waveform from the human scalp following a 500 ms stimulus of eucalyptol with component latencies of 270–350 ms, 410–500 ms and 520–620 ms, respectively. Analysis of the 'area under the curve' during uni-

lateral stimulation revealed that N1 was maximal in the contralateral central region and N2 was maximal in the ipsilateral precentral region. Thus, both olfactory and somesthetic (or trigeminal) components are distinguishable in the olfactory evoked potential.

More recently, olfactory evoked potentials have been reported in 20 patients with well-defined lesions of the central nervous system and trigeminal nerve (Westhofen *et al.*, *Laryng Rhinol Otol* 1985, 64:378-387). This evoked potential was characterized by two positive peaks with latency ranges of 100-250 ms and 350-500 ms. Interruption of the ophthalmic division of the trigeminal nerve eliminated the first component whereas isolation of the maxillary and mandibular divisions produced no change. Lesions of the basal ganglia and brainstem were accompanied by absence of the first component. The second component was affected by lesions of the temporal or frontobasal cortex. Massive lesions of the temporoparietal cortex were associated with the loss of both components over the damaged hemisphere and occasionally over the contralateral hemisphere. Midline and frontal lesions produced no change in the evoked potential. The small number of patients does not allow conclusions on the specificity of these changes in evoked potential. Unfortunately, only one average was documented for each patient, raising questions about the reliability of the evoked potentials.

Tonoike [16] has used 'time-varying filtering' to analyse power spectra of olfactory evoked potentials in human subjects elicited by 200 ms presentations of amyloacetate, vanillin and d,l,levo-camphor. The frequency band up to 8 Hz was found to be the primary contributor to the olfactory evoked potential signal, whereas the characteristic frequency for noise was maximized at 20 Hz. This tends to confirm that the major component of the olfactory evoked potential is a rather sustained wave form, even though a number of methodologic questions remain.

Conclusion

Objective and quantitative measures of olfaction must be developed in order to better understand the role that olfactory processes play in memory and behavior. Olfactory evoked potentials could provide such a quantitative measure but a number of problems with stimulus delivery must be addressed. It is unknown whether olfactory deficits in dementing illness are due to disease-specific changes in the olfactory pathways or if these deficits

are a non-specific manifestation of the dementing process. Nonetheless, existing methods of olfactory testing easily performed in the office setting may be helpful in differentiating dementia from the 'pseudo-dementia' of depression. Ongoing research to discover specific olfactory deficits in different diseases is likely to provide a more powerful clinical tool in the near future.

Annotated references and recommended reading

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Abbreviation

DAT, dementia of the Alzheimer type.