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Olfaction and Psychiatry

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Recent clinical studies have identified significant olfactory deficits in several neuropsychiatric disorders, notably Alzheimer's disease and Parkinson's disease. These have correlated with neurochemical and neuropathological studies of the olfactory system. The presence of a specific sensory deficit may be related to the localisation of pathology within the brain. There is a need for incorporation of olfactory testing into routine clinical examination.

Olfaction has often been regarded as the "Cinderella of the senses" (Moore-Gillon, 1987). The clinical significance of the sense of smell and its disturbances has been neglected and there has been little research into the normal mechanisms or pathophysiology of smell perception by comparison with that devoted to sight or hearing.

However, recently there has been increased interest in both clinical and neuropathological aspects of olfaction, with particular consequences for psychiatry. It is important to identify the relationship of such a sensory deficit to the search for localisation of cerebral disease processes; similarly it will be necessary to incorporate into clinical practice any new developments which might add to the confidence with which diagnoses can be made.

Organisation of the olfactory system

Primary olfactory neurons arising in the nasal sensory epithelium form the olfactory nerves which pass through the cribriform plate to terminate in the glomeruli of the olfactory bulb. Here they make contact with neurons (the mitral cells) which give rise to fibres forming the olfactory tract. Mitral cell axons pass to several sites: numerically the greatest termination occurs in the pyriform cortex and adjacent corticomedial amygdala, which together form the uncus. Less heavy terminations are found in the ventral striatum (homologous to the olfactory tubercle in sub-primates), the ventromedial hypothalamus and the anterior olfactory nucleus, from where fibres pass to the contralateral bulb (Meyer & Allison, 1949; Powell *et al*, 1965; Switzer *et al*, 1985).

From these primary recipient zones, olfactory information passes to many other brain regions. The pyriform cortex projects to the thalamus (mediodorsal and medioventral nuclei) and thence to orbitofrontal and dorsolateral frontal cortex (Powell *et al*, 1965; Kievit & Kuypers, 1977; Krettek & Price, 1977; Potter & Nauta, 1979); the pyriform cortex also sends fibres to other temporal cortical areas and to the insula. It is uncertain which parts of olfactory processing are served by each pathway. It seems likely, however, that the projection to dorsal thalamus and frontal cortex, which is the major *neo*cortical olfactory representation, is involved with odour discrimination (Tanabe *et al*, 1975; Slotnik & Kaneko, 1981; Eichenbaum *et al*, 1983*b*; Staubli *et al*, 1987), cognitive aspects (Potter & Butters, 1980) and convergence with visual (Cavada, 1984) and taste (Benjamin & Akert, 1959) modalities. Olfactory pathways to the hypothalamus, which are multiple, are thought to contribute to eating and reproductive behaviour; pathways between the frontal lobes and hypothalamus may in some way integrate these functions (Nauta, 1971), although the existence of direct fronto-hypothalamic connections is uncertain (Brodal, 1981). It is unclear whether the spread to the hippocampus and to temporal cortex plays a different role from that to the frontal regions, clinical effects of lesions in both sites being similar (Rausch & Serafinides, 1975; Potter & Butters, 1980); however, hippocampal lesions may produce a greater olfactory memory defect (Staubli *et al*, 1984). As in other sensory systems, there is centrifugal modulation of olfactory input. Efferent fibres from the uncus are prominent (Powell *et al*, 1965); they terminate primarily in the olfactory bulb, which also receives centrifugal projections from the cholinergic basal forebrain (Price & Powell, 1970; Jones *et al*, 1976), locus ceruleus and raphe nuclei (Switzer *et al*, 1985).

Factors affecting olfactory performance

Before olfactory involvement in neuropsychiatric disease is discussed, certain variables which may affect olfactory function should be mentioned. Any inflammation or occlusion of the nose is likely to raise smell detection thresholds, and may persist for several weeks (Elsberg *et al*, 1935; Schiffman, 1983), so interfering with clinical testing. Smoking causes similar functional impairment, acting both through

increased mucosal secretions and degeneration of the olfactory mucosa (Joyner, 1964; Doty *et al*, 1984).

The effect of ageing is particularly important in view of the findings in Alzheimer's disease (AD) and Parkinson's disease (PD) to be considered below. It is now well established that ageing is associated with a marked impairment in odour detection (Chauhan *et al*, 1987; but see Serby *et al*, 1985), intensity estimation (Enns & Hornung, 1988), identification (Schemper *et al*, 1981; Doty *et al*, 1984) and memory (Cain & Murphy, 1987). This decline with age correlates with significant degeneration of the olfactory epithelium (Smith, 1942), and of sensory neurons in the olfactory bulb (Bhatnagar *et al*, 1987), and may also relate to degeneration in central olfactory structures (e.g. Herzog & Kemper, 1980).

Another potential variable is the contribution to chemoreception made by the fifth cranial nerve. Free trigeminal nerve endings in the olfactory mucosa play a major role in perception of, and response to, irritant odours. This has been demonstrated experimentally (von Buskirk & Erickson, 1977) and in anosmic patients (Doty *et al*, 1987*a*); for example, butanol, used as an olfactory test substance, causes a marked trigeminal response (Laing, 1985). The interaction between smell and taste – apparent to any gourmet – is now being appreciated, and occurs at both peripheral (Bouvet *et al*, 1987) and central levels (Benjamin & Akert, 1959; von Buskirk & Erickson, 1977; Cain & Murphy, 1980). As a result, studies purporting to be testing purely olfactory function need to be read critically.

Olfactory changes in neuropsychiatric disorders

Alzheimer's disease

The first clinical suggestion of olfactory involvement in AD came with observations of cranial nerve function in senile dementia (Waldton, 1974). Since then, a number of reports have confirmed and extended these findings (Serby *et al*, 1985; Knupfer & Spiegel, 1986; Warner *et al*, 1986; Doty *et al*, 1987*b*; Rezek, 1987; Koss *et al*, 1988). All these studies demonstrate a marked impairment of smell identification in early AD compared with that of age-matched controls, and most also show an increased threshold for odour detection, although Koss *et al* (1988) did not find this (see also St Clair, 1984). Knupfer & Spiegel (1986) reported a greater olfactory deficit (detection, identification and naming) in AD than in cognitively similar cases of multi-infarct dementia, both groups performing worse than controls. This suggests a role for olfactory testing in differentiating AD from multi-infarct dementia, and might improve upon the Hachinski index in this regard. However, confirmation of these findings would be valuable as the controls were significantly younger than the demented groups, sex ratios were different and cognitive functions not well matched. Furthermore, as with the other studies mentioned, no pathological confirmation of diagnosis was made. The well-controlled study of Doty *et al* (1987*b*) found marked detection and identification deficits in mild AD, and, moreover, only 2 out of 34 cases were aware of their deficits, a feature not explicable by their cognitive impairment.

Recent neuropathological studies have correlated well with these clinical findings. The anterior olfactory nucleus in AD contains senile plaques, neurofibrillary tangles and reduced cell counts (Averback, 1983; Esiri & Wilcock, 1984), and the olfactory bulb also shows involvement (Esiri & Wilcock, 1984; Ulrich, 1985; Ohm & Braak, 1987), as does nasal sensory epithelium (Talamo *et al*, 1989). Associated with these morphological changes is a markedly reduced cholinergic activity in the ventral striatum (Simpson *et al*, 1984), which in common with other olfactory areas has a rich cholinergic innervation (Halasz & Shepherd, 1983). Moreover, central olfactory structures are heavily affected by AD, especially the amygdala and the entorhinal, pyriform and temporal cortices (Harrison, 1986; Pearson & Powell, 1989). It is unclear which of the lesions is most clinically significant to olfaction; it is possible that peripheral involvement (olfactory bulb and anterior olfactory nucleus) accounts for the increased detection threshold, whereas central lesions explain the identification and naming deficits. This is in agreement with the type of olfactory deficits seen in Korsakoff's psychosis (KP), mentioned below, and in temporal lobe lesions; the latter cause impaired identification and recall but do not affect detection (Rausch & Serafinides, 1975; Eichenbaum *et al*, 1983*a*).

Parkinson's disease

Odour detection (Ansari & Johnson, 1975; Ward *et al*, 1983; Quinn *et al*, 1987; Doty *et al*, 1988) and identification (Ward *et al*, 1983; Serby *et al*, 1985; Doty *et al*, 1988) are significantly impaired in PD, and represent one of the few definite sensory changes in the condition. Ansari & Johnson (1975) found this to be related to a rapid disease course, but this finding has not been replicated in later studies. The impairment appears to be independent of variables such as age, sex, medication and ratings of neurological function (Doty *et al*, 1988).

As with AD, attempts have been made to correlate the clinical picture with neurochemical and neuropathological features. Not surprisingly, in PD this has focused on dopaminergic changes (Ward *et al*, 1983), including dopamine content in the olfactory tubercle and bulb (Fallon & Moore, 1978), and in mesolimbic pathways (Javoy-Ajid & Ajid, 1980), although Quinn *et al* (1987) point out that cholinergic and glutamatergic systems could also be involved. Clinico-pathological correlations in PD are hampered by the complex relationship with AD (Quinn *et al*, 1986), and it is unclear whether the olfactory deficits in PD and AD share the same cause (Doty *et al*, 1988).

Korsakoff's psychosis

Patients with KP exhibit impaired odour detection, identification and intensity estimation when compared with non-KP alcoholics and normal controls (Jones *et al*, 1975*a*,*b*; Potter & Butters, 1980; Mair *et al*, 1986). These deficits are modality-specific and not explicable by short-term memory loss or intellectual impairment, as concurrent memory testing (Jones *et al*, 1975*a*) or other sensory identification tasks (Mair *et al*, 1986) were performed successfully. The difference in results between alcoholic KP patients and non-KP alcoholics makes it unlikely that the deficits result from trauma to the olfactory nerve.

Degeneration in the mediodorsal thalamic nucleus is the most consistent candidate neuropathological lesion in KP, and has been advocated to explain the olfactory changes, together with atrophy in the prefrontal areas to which it projects (Potter & Butters, 1980; Mair *et al*, 1986). This is supported by the reduced odour discrimination seen in experimental and clinical lesions of the prefrontal cortex mentioned previously. However, intralaminar nuclei and other sites may also be involved (Mair *et al*, 1986). Neurochemically, attention has centred on the reduced noradrenergic function in KP (McEntee *et al*, 1984), which also occurs in AD and PD (Gottfries & Roos, 1969), and which has been invoked to explain the olfactory deficits in all these conditions (McEntee *et al*, 1984).

Other neuropsychiatric disorders

There are preliminary reports of olfactory changes in schizophrenia, Huntington's chorea, Down's syndrome, and depression.

Impaired olfactory discrimination has been reported in schizophrenics when compared with medication-matched non-schizophrenic patients (Hurwitz *et al*, 1988). This phenomenon appears to be independent of psychopathological differences. Olfactory changes are perhaps not unexpected in schizophrenia, given the occurrence of olfactory hallucinations as a symptom, and the evidence linking both to temporal lobe dysfunction (Rausch & Serafinides, 1975; Roberts, 1988). It has also been found that schizophrenic men have a higher olfactory sensitivity to androsterone, a pheromone, than normal men, a difference not seen in women (Bradley, 1984). This may relate to altered sex steroid excretion profiles in male schizophrenics (Brooksband & Pryse-Phillips, 1964).

Patients with early Huntington's chorea may have impaired short-term olfactory memory, in the absence of equivalent visual or auditory deficits (Moberg *et al*, 1984). There are also symposium reports of reduced odour detection and discrimination in depression (see Serby, 1987), although this is controversial (Amsterdam *et al*, 1987) and, like the findings in schizophrenia and Huntington's chorea, awaits confirmation and further study. Finally, olfactory deficits have been reported in Down's syndrome (Warner *et al*, 1988), which is of interest given its relationship with AD (Mann, 1988). The various olfactory changes identified in neuropsychiatric disorders are summarised in Table I.

TABLE I
Olfaction in neuropsychiatric disease

	Odour detection[1]	*Odour identification*[1]	*Odour memory/recall*[1]
Alzheimer's disease	(−)	−	−
Parkinson's disease	−	−	?
Korsakoff's psychosis	−	−	−
Temporal lobe lesions	N	−	−
Frontal lobe lesions	N	−	?
Schizophrenia	?	(−)	?
Huntington's chorea	?	?	(−)
Depression	(−)	(−)	?
Down's syndrome	?	(−)	?

1. N = normal; − = clear deficit; (−) = possible deficit; ? = unknown.

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Mechanisms of olfactory involvement in psychiatric disorders

The evident frequency of olfactory symptoms and signs in neuropsychiatric disorders suggests that their association is not coincidental. At present, the data provide only coarse indications of such olfactory deficits, and, to some extent, a lack of clinical sophistication limits pathological correlations. This may account for the lack of any coherent explanatory theory for olfactory involvement in psychiatric disease, with separate mechanisms proposed for each disorder; for example, acetylcholine and the olfactory bulb in AD, and noradrenaline and the mediodorsal thalamus in KP.

In principle there appear to be three main ways in which olfaction and neuropsychiatric disease may be inter-related.

First, the identification of a specific sensory deficit of this kind may help to localise pathology, a psychiatric goal which has largely remained elusive. This may become possible by more detailed correlation of sites of neuropathological involvement with types of olfactory deficit, or by a search for specific pathology indicated by clinical observation. For example, if impaired odour discrimination, but not detection, is found to coexist with pathology in the orbitofrontal cortex, then clinical identification of such a deficit will suggest disease involvement in that brain region. Correlations of this kind will require clear delineation of types of olfactory deficit, as well as separation of sensory from cognitive parameters of olfactory function. Olfactory evoked potentials, should they become available, would be valuable as an investigative tool (Moore-Gillon, 1987), particularly in AD where there are abnormal visual (Orwin *et al*, 1986) and auditory (Neshige *et al*, 1988) evoked potentials.

Secondly, the likely significance of detailed olfactory testing becomes apparent in a number of ways. It may prove that olfactory changes are present early on in disease – as is the case for AD – and might even pre-date overt psychiatric symptomatology. Olfactory testing may thereby enable earlier diagnosis and treatment. It may also be useful for differential diagnosis, such as distinguishing AD from multi-infarct dementia. Furthermore, clinical research might identify currently unknown disease subtypes with regard to olfactory involvement; for example, only a proportion of PD patients exhibit symptoms which bring them to the attention of psychiatrists. These patients might prove to be the subgroup of PD with olfactory deficits, the two features being linked by involvement of areas additional to those producing a purely motor disorder (e.g. via nigrothalamic connections or mesolimbic dopaminergic pathways). Such studies could also investigate whether olfactory changes relate to subtypes of other disorders, including depression and schizophrenia.

Thirdly, involvement of the olfactory pathways may have significant implications for disease aetiology. The possibility of nasal entry of a pathogen is currently under scrutiny for AD (Pearson *et al*, 1985; Perl & Good, 1987; Mann *et al*, 1988; Pearson & Powell, 1989) and PD (Langston, 1985). Candidate environmental toxins of this kind include aluminium (Roberts, 1986), solvents (Freed & Kandel, 1988), and pesticides (Tanner, 1989). Experimental studies have shown that significant uptake of materials occurs from nose to brain, and from the blood to the brain via leaks in the olfactory mucosa (Shipley, 1985; Balin *et al*, 1986). Both intra- and extra-cellular pathways are implicated, and constitute important breaches of the barrier between the brain and the external environment. Because of the fibre terminations of monoaminergic and cholinergic fibres in the olfactory bulb, this also represents a possible mechanism by which such structures could be involved in neuropsychiatric disease (see Hardy *et al*, 1986).

It is unclear whether the involvement of the brain areas discussed represents a vulnerability of these regions, or is merely *de facto* support for the view that dysfunction of such areas underlies psychiatric and olfactory symptomatology (see McKenna, 1987). The suspicion that a vulnerability of some kind exists has been discussed in terms of phylogenetic age: areas such as the brainstem, amygdala and pyriform cortex are considered to be pre-mammalian structures, and as such are postulated to be liable to degeneration or disease (Rossor, 1981). Alternatively, pathological processes might have a predilection for the connections from such areas to the neocortex, an evolutionary gap bridged by olfactory pathways (Reep, 1984). However, as mentioned, it is not *a priori* necessary to postulate any specific vulnerability to explain links between olfaction and psychiatric disease.

Clinical implications

Specific alterations in smell detections, identification and memory are present in a number of the major neuropsychiatric diseases (Table I). In consequence, the clinical evaluation of olfaction should become an integral part of the psychiatric assessment. Tests of olfactory function are particularly indicated in suspected dementia, where identification of deficits

may be a valuable differential diagnostic sign, and such deficits may prove to antedate gross cognitive changes; tests will become more important with the advent of palliative therapy for AD. Biopsy of nasal sensory mucosa may also have a diagnostic role given the findings of Talamo *et al* (1989). Assessment should include direct questioning as well as inquiry into taste perception and enjoyment of food – as patients may be unaware of anosmia – and should be followed by clinical testing. Concurrent or recent respiratory infection or coryza should be noted and, if present, testing should be postponed or repeated when the nasal airway is clear. A smoking history should be taken and past head injury documented.

For testing, a set of fresh smell bottles is required, and examination is carried out to investigate both detection and identification. The traditional method of olfactory testing is not wholly satisfactory, especially for detection thresholds (Pinching, 1977; Moore-Gillon, 1987), but should pick up most deficits. For research purposes, the development of standardised test procedures (for example the UPSIT (Doty *et al*, 1984)) has been an important advance, as studies have used different protocols without standardisation or validation (see Chauhan *et al*, 1987; Serby, 1987). Other flaws which have affected such work include small sample sizes, poorly matched control groups, and failure to allow for the trigeminal contribution. These factors point to the need for repeated studies using larger groups and better methodology. Differentiation of deficits of detection from those of identification and memory must also be improved, particularly with regard to AD and PD, where subtle cognitive problems may compound the difficulty of interpreting test results.

It is likely that the olfactory system will continue to increase in importance to psychiatry: as part of the clinical assessment, in terms of a possible pathway for disease progression, as an aid to the identification of localised pathology, and potentially as a route for delivery of therapeutic agents.

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