Commentary

Is Parkinson’s disease a primary olfactory disorder?

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Summary

It has been known for over 30 years that olfactory function is disordered in idiopathic Parkinson’s disease (IPD). The severity and partial specificity of anosmia was not realized until recently, with the advent of more detailed analysis and sophisticated measurement. The olfactory vector hypothesis suggests that the causative agent for IPD enters the brain via the nasal route, but the reason for olfactory dysfunction may be more subtle. Evidence for olfactory disturbance is reviewed from pathological, psychological, neurophysiological and genetic standpoints. It is proposed that the initial causative event in IPD may start in the rhinencephalon (olfactory brain) prior to damage in the basal ganglia.

Introduction

It is well established that many neurodegenerative diseases are associated with impaired sense of smell, including Alzheimer’s disease, Huntington’s chorea, and multiple system atrophy (Table 1). The majority of patients with idiopathic Parkinson’s disease (IPD) have defective smell sense, although this is still not widely appreciated. To make plausible a theory that the condition is primarily olfactory, there needs to be evidence that the olfactory system is consistently and severely involved to a degree equaling or exceeding that of the classical motor triad of tremor, rigidity and akinesia. Furthermore, a mechanism of secondary motor involvement needs to be demonstrated. Evidence in support is presented in this article.

Pathological evidence

The basal ganglia have been intensively studied in PD, but the rhinencephalon has not been investigated systemically. In an examination of four Parkinson’s disease (PD) patients with dementia, one brain showed Alzheimer-type change in the amygdala, adjacent anterior temporal cortex and CA2 sector of the hippocampus. The hippocampus was normal in the remaining three. It is uncertain whether all central olfactory areas were examined; furthermore the cases were complicated by the presence of dementia. More recently, we examined ‘blind’ to clinical information, the olfactory bulbs and tracts from formalin-fixed brains of eight controls and eight patients with a clinical and pathological diagnosis of IPD taken from the UK Parkinson’s Disease Brain Bank. By inspecting the olfactory bulb and tract, all eight cases were correctly diagnosed ‘probable PD’. Lewy bodies were most numerous in the anterior olfactory nucleus, but they were also found in mitral cells. Cortical Lewy bodies, mainly in the anterior cingulate gyrus and parahippocampus, were also plentiful in two patients. It was subsequently shown that the loss of anterior olfactory neurons correlated with disease duration. The pathological evidence confirms the presence of cellular damage characteristic of PD in the olfactory bulb and hippocampus.
Table 1  Relative degree of olfactory impairment in various degenerative diseases

<table>
<thead>
<tr>
<th>Olfactory impairment</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>++++</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>++++</td>
</tr>
<tr>
<td>Parkinsonism-dementia complex of Guam</td>
<td>++++</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>+++</td>
</tr>
<tr>
<td>Huntington’s chorea</td>
<td>++</td>
</tr>
<tr>
<td>Motor neuron disease</td>
<td>+/-</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>0</td>
</tr>
<tr>
<td>Corticobasal degeneration</td>
<td>0</td>
</tr>
<tr>
<td>Essential tremor</td>
<td>0</td>
</tr>
</tbody>
</table>

Key to olfactory impairment: ++++, very severe; ++++, severe; ++, moderate; +, mild; 0, normal.

The relative degree of central versus peripheral involvement has not yet been determined pathologically, nor has it been shown whether there are Lewy bodies in the neurons of the nasal olfactory epithelium.

Smell identification evidence

The first large-scale olfactory study was by Doty and colleagues\(^4\) using the University of Pennsylvania Smell Identification Test (UPSIT).\(^5\) This uses microencapsulated odorants that are released on scratching the strip with a pencil. There are 40 different odors, and a forced choice is made from four possible answers. Olfactory dysfunction was unrelated to odor type, did not depend on disease duration, and did not correlate with motor function, tremor, or cognition, in keeping with an earlier study.\(^6\) Doty’s group\(^7\) also demonstrated that the deficit was of the same magnitude in both nostrils, and was uninfluenced by anti-Parkinsonian medication. In their largest study\(^8\), based on 180 IPD patients, they defined cut-off scores for discriminating controls from PD patients, e.g. a male of 60 years who scored 31 or less might be suspected of having the disease.

We undertook a comparable survey\(^9,10\) using UPSIT on healthy members of Hospital and British Telecom staff. All patients had IPD, although the fallibility of such classification is about 16%.\(^11\) There were 155 PD cognitively intact, non-depressed patients aged 34–84 years, and 156 controls aged 17–90 years. The UPSIT scores for PD patients were significantly lower than controls. Only 19% (30/155) of the PD patients had a score within the level expected for 95% of our age-matched healthy controls (Figure 1). There were 65 (42%) who were anosmic, i.e. scoring <17. There was no correlation between disease duration and UPSIT score (r = 0.074), in keeping with earlier work.\(^4\) While there is a background depression of olfactory identification, superimposed upon this we found a degree of selective odor deficit.\(^12\) Odors most readily misidentified by PD patients on the UPSIT test were lemon, pizza, wintergreen, rose and clove. Pizza was the best single discriminant odor, with pizza and wintergreen in combination superior still. Thus a subject could be suspected of having PD if both pizza and wintergreen were inaccurately identified and would probably not have the disease if both of these odors were positively smelt correctly (i.e. not by random guessing). Because patients made a forced choice from four possibilities, 25% will be correct by chance alone. Hence our sensitivity value of 76% for pizza in the presence of 90% specificity infers anosmia to ‘UPSIT-pizza’ odor for PD patients. Pizza is a complex odor, with oregano as the most distinguishing characteristic. In turn oregano is a highly complex mix of several organic chemicals.

It is intriguing that all six patients with MPTP parkinsonism had normal smell sense\(^13\) when evaluated by UPSIT and olfactory threshold tests. If the olfactory vector hypothesis is correct (q.v.) then

![Figure 1. UPSIT score plotted against age. Control data consists of 156 healthy individuals (continuous line) plotted against 155 patients with IPD. Control 95% CIs are shown as dashed line. Individual scores for IPD group are represented by ‘+’ symbol.](image-url)
damage to the olfactory system by intravenous toxins might not be expected. Furthermore MPTP-induced parkinsonism is significantly different from IPD on clinical and pathological grounds.

**Neurophysiological evidence**

We tested 73 patients with IPD by olfactory evoked potential (OEP) recording. In 36 (49%), responses were either absent or unsatisfactory for technical reasons. Regression analysis on the 37 with a measurable trace showed that for hydrogen sulphide (H₂S) a highly significant latency difference existed between diagnostic groups (i.e. control or PD). Assuming that the 36/73 who had no detectable OEP were abnormal and combining this with the abnormal 12/37 (32%), 81% had an abnormality on OEP, which is the same as for UPSIT measurements. In 10 patients with normal UPSIT scores, there was one with absent H₂S responses and three with significantly prolonged latency to H₂S. Responses were not obtained in about half the patients tested, but this is not surprising since they had a poor sense of smell generally and the small number of delayed H₂S responses in those we could test may be a reflection of a healthier population in the olfactory sense. A record labelled absent may in fact contain a response below the limit of detection imposed by averaging, in our case, just 16 signals. We used only one odour, whereas the UPSIT implements 40. If a large number of different gases were used, the sensitivity of OEP might well increase.

Similar results were subsequently obtained in 31 patients with PD tested by OEP to vanillin and H₂S. Responses were obtained to both stimulants in all patients. Prolonged latencies were seen in the PD patients, whether they were taking medication for the disease or not. More marked changes were seen in those on treatment, however. The same group demonstrated for the first time a correlation between disability (as measured by Webster score) and latency to H₂S OEP.

Viewed alone the UPSIT result places 81% of patients outside the 95% limit for controls. When this information is combined with OEP data (4/10 abnormal where UPSIT score was normal) the fraction of olfactory abnormality approaches 90%. Such frequency is higher than that of tremor, which is usually quoted at 70% and nearly equals that of rigidity and akinesia. At least for a hospital population, olfactory dysfunction is common and potentially as important as the cardinal motor signs of PD. It is possible that patients with a normal UPSIT score had a parkinsonian syndrome such as progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration etc. and, if so, abnormality on olfactory tests may be even more specific.

**Genetic evidence**

Although it awaits confirmation, our UPSIT study infers there may be an inherited specific anosmia to some of the chemicals that give pizza (oregano?) and perhaps wintergreen their distinguishing characteristics. Anosmia to perhaps one component of these odors might remove an individual’s ability to identify it. Our observations on selective odor defects in UPSIT raise the possibility of congenital or acquired selective hyposmia in PD—comparable to androgenone smell blindness, which affects 20%–47% of healthy individuals. Of particular relevance is an experiment in which rats were exposed to 44 inhaled vapours for several weeks. For each odor, there was a selective pattern of mitral cell loss in the olfactory bulb, unrelated to odor concentration. It is conceivable that olfactory damage in PD may be caused by exposure to a neurotoxic vapour, which selectively injures part of the olfactory system. Speculatively, one could ‘work back’ from the olfactory bulb pathology and describe the chemical characteristics of a possible neurotoxin. Alternatively if there is indeed a congenital inability to smell certain odors, they might be inhaled inadvertently and repeatedly. If the specific anosmia relates to a neurotoxin such as pyridine, then damage to distal and thereafter central parts of the olfactory pathway might result.

In the majority of patients, IPD is a sporadic condition. Estimates from large community-based case-control studies suggest that just over 1% first-degree relatives will have the same condition. There are clear instances of autosomal dominant PD with large pedigrees and pathological confirmation. Recent evidence from Italian and Greek kindreds has demonstrated a point mutation of the gene coding for α-synuclein. Rat synucleins show considerable homology with the human counterpart. By in situ hybridization it was shown that the three varieties of synuclein mRNA were expressed in discrete areas. Strongest expression (+ + +) was in the lateral olfactory tract, hippocampus, dentate gyrus, habenula and pyriform cortex. The olfactory bulb was graded (+ + +) and less expression was seen (+ + ) in caudate-putamen, substantia nigra, dorsal raphe nuclei and granular layer of the cerebellum. The areas of major expression of synuclein in human brain are not yet characterized, but the pattern in the rat at least, corresponds to primary olfactory areas, with the strianigral system very much in second place.
Mechanism of damage

Why is a movement disorder such as PD so consistently associated with hyposmia? The olfactory identification defect in PD is similar to AD;28 there is profound disturbance of cognition in AD, but much less in PD, and the olfactory tests in PD have all been done in patients with normal cognitive function. One possibility is that a virus or chemical agent that gains entry to the CNS via the nose causes PD. Indeed this theory has been raised previously to explain both Alzheimer’s disease24–26 and (briefly) for PD.27

Nasal entry of virus or chemical

HSV1 virus placed intra-nasally in 6-week-old mice was detectable in the trigeminal root entry zone and olfactory bulbs 4 days later.28 In some mice, virus which had entered the olfactory bulb spread as far as temporal lobe, hippocampus and cingulate cortex. Horseradish peroxidase (HRP) applied intranasally can be transported to the bulb, anterior olfactory nuclei and to transmitter-specific projection neurones from the diagonal band (cholinergic), raphe (serotonergic), and locus coeruleus (noradrenergic).29 Because a large macromolecule such as HRP can spread so easily, it may be argued that environmental contaminants and perhaps drugs of abuse could gain relatively unimpeded access to the entire nervous system. It is not widely appreciated that there are significant and direct connections between primary olfactory areas and substantia nigra (SN). Application of horseradish peroxidase into the olfactory tubercle results in anterograde labelling of the ipsilateral ventral tegmental area (VTA), SN pars reticulata as well as the ventral pallidum and anterior olfactory nucleus.30 There was as expected, retrograde labelling in the ipsilateral olfactory bulb, anterior olfactory nucleus and other primary olfactory areas. Because the ventral striatum (VS), i.e. olfactory tubercle and nucleus accumbens, receives many projections from the limbic system, it is suggested that VS is concerned with integrating limbic information into the striatal system.

A further possibility relates to the fact that inhaled solvents such as trichloroethylene may rekindle activity in latent viruses such as herpes simplex.31 Support for the nasal-entry theory might be strengthened if there was a correlation between the olfactory and motor deficits—either in terms of symptom severity or duration. This has not been found clinically,4 but there is probably a correlation between neuronal loss in the olfactory bulb and disease duration.3 At present, the possibility that individuals with anosmia later develop PD awaits proof. One could argue that PD is caused by a single major CNS insult and that any progression is simply due to age-related neuronal loss in SN.32

Defective P450 cytochrome

In some PD patients, there is a mutation in the P450 cytochrome CYP2D6-debrisoquine hydroxylase gene.33 Mammalian P450-dependent oxygenases provide a central line of defence against exogenous toxins, and it has been shown that the risk of PD is higher in those with a P450 genetic polymorphism associated with deficient debrisoquine metabolism. Whilst the high concentration of P450 in hepatic microsomes is well known, it has also been shown that microsomes in the olfactory epithelium of, for example, the rat44 and rabbit35 have high levels of P450. These are sometimes in excess of those in the liver, depending on the particular subtype. The olfactory bulb of the monkey has particularly high P450 levels compared to other parts of its brain. There are variable levels of P450 in the rest of the CNS, but most areas are incompletely characterized. Numerous volatile compounds are readily absorbed by the nasal mucosa.45 Many non-volatile materials such as environmental pollutants can reach the nasal mucosa, probably by adsorption on to small particles in the air that deposit on the nasal epithelium.37 Compounds absorbed by the nasal mucosa are actively metabolized in situ, sometimes detoxified, or they may be activated to become more toxic or carcinogenic.36,39 Compounds that have been shown to be metabolized in vitro by the nasal P450-dependent monoxygenase system include nasal decongestants, essences, anaesthetics, alcohols, nicotine, cocaine and many nasal carcinogens.40 Herbicides such as dioxins41 or chlorthiamid,42 whether administered intravenously or intraperitoneally, are selectively taken up by, and harmful to, the olfactory epithelium. The CNS distribution of CYP2D6 is not known, but if it were to be concentrated in the basal ganglia and olfactory pathways, the pathology at these sites might be explained. Other cytochrome systems may be defective in PD, while it is possible of course that the external agent, if there is one, gains entry to the brain via the blood route.

Phylogeny of olfaction

Another explanation can be built upon the phylogeny of the olfactory system. In the reptile, the entire pallial field is olfactory. In the tortoise, there is a small area of non-olfactory differentiated cortex, which is still under olfactory control. In the opossum, the hippocampus and pyriform cortex is well developed, and still more extensive than the non-olfactory cortex (neopallium), while in the human
the neopallium is massive and crowds out the olfactory cortex. A structure such as the hippocampus that is concerned with olfaction in lower species is well developed in humans, but only part of its function is olfactory. It is possible that a highly conserved gene may have a multiple role in olfaction, movement, and cognition. It has been suggested recently that cells expressing netrin (an axon guidance molecule) or ddc (the deleted in colorectal cancer gene) may control cell migration in the developing cerebellum, optic nerve and olfactory epithelium and the establishment of connections to SN and corpus callosum.43 As mentioned above, a mutation in the alpha synuclein gene is responsible for one form of autosomal dominant PD, and expression is strong in rat primary olfactory areas, much more so than the caudate-putamen and substantia nigra. This gives evidence at genetic level of a link between the olfactory and extrapyramidal systems.

Phylogenetically, olfaction, movement and autonomic control appear to be linked, and it is thus plausible that all would fail together in PD because of a common defect in a highly conserved gene.

Disease specificity of hyposmia

Parkinson’s disease is not the only neurodegenerative condition associated with olfactory disorder. Hyposmia of similar degree is found clinically and pathologically in Alzheimer’s disease.24 It should be emphasized that all patients with PD tested by us and others had, by design, no evidence of cognitive impairment. Varying degrees of hyposmia occur in allied conditions as shown in Table 1. It is of interest that patients with benign essential tremor (reference 44 and own observations) have intact sense of smell. Conversely, one might wish to review a diagnosis of IPD in someone with a normal UPSIT score. Hyposmia is thus not specific, merely characteristic of IPD. By the same token tremor, rigidity and akinesia are all non-specific findings in PD, but we prefer to define the disease by its motor rather than sensory features.

Debate continues whether the aetiology of PD is genetic, environmental, or genetic susceptibility to an environmental agent. A large study of 193 male twin pairs has shed new light on this area. In brief, the overall concordance ratio of monozygous to dizygous twins was similar, implying weak genetic factors. Subgroup analysis of 16 pairs in whom onset was under 50 years showed 100% concordance rate in monozygous twins. In the remaining 12 dizygous pairs, there were just two concordant pairs, giving a high heritability index of 0.94. This suggests that genetic factors are strong in those with young age of onset. The twin study implies that for the majority

with late-onset disease, genetic factors appear less important, and if so an olfactory neurotoxin would remain a possible pathogenic mechanism.

Conclusions

There is much to suggest that a chemical toxin may cause PD. PD induced by drugs (e.g. phenothiazines) may be clinically indistinguishable from IPD and may last several months even after removal from exposure. Methyl-phenyl-tetrahydropyridine causes a severe and persisting form of PD in man and animals, and has structural similarity to the herbicide paraquat. There are isolated reports of parkinsonism following exposure to this although it is doubted whether inhaled or ingested paraquat can enter the brain in sufficient quantity to cause damage.47 Nonetheless, many retrospective case control studies suggest increased risk of PD if there is history of exposure to pesticides.48 If PD is shown to relate to environmental exposure, then the significance of contact with agrochemicals assumes great importance in view of the ability of many such compounds to damage the sense of smell.

Given that the olfactory system in IPD is devastated, what evidence suggests that this is not of relevance, i.e. that the smell loss is an epiphenomenon of no etiological importance? (i) Clinical. About 20% of those with a clinical diagnosis of IPD have normal smell identification. If hyposmia were a prerequisite for the diagnosis, the argument is weak. Conversely not all those with a clinical diagnosis of IPD have rigidity, some have no tremor, and others have no akinesia. It is suggested that tremor is present in 70%, with rigidity or akinesia in 90%.16 As mentioned above, we tested by OEP. 10 patients with a diagnosis of IPD who had normal UPSIT scores and of these, four had absent or delayed OEP, which implies that UPSIT does not test (nor would it be claimed to test) all aspects of the olfactory pathway. Pathological studies suggest that the diagnostic error rate for IPD is 16% or more11 and as mentioned already, olfactory identification is abnormal in some parkinsonian syndromes (Table 1). It is not yet known whether those with normal UPSIT score are the very patients who have an incorrect diagnosis. Patients with MPTP-induced PD have normal smell sense. In some ways this would be expected, as the agent is given intravenously, and there are significant differences in the clinical and pathological features of this disease from the spontaneous variety. There are no studies of olfactory function in phenothiazine-induced PD but one would predict a normal result. (ii) Smell identification and OEP. While there is agreement about the severity of olfactory loss in IPD, there was thought to be no
correlation of such deficit with the duration, severity or type of disease. Initial studies implied no correlation between severity of disease and olfaction, but it has now been suggested that there is a correlation between disability (Webster score) and olfactory evoked response latency. There seems to be no progression of smell identification with time and there is only anecdotal evidence that impaired smell sense precedes the illness. At pathological level, however, it has been shown that the number of neurons in AON decreases significantly with time. There may be a pathological change therefore which is not necessarily reflected in the clinical tests, or the tests may not be sufficiently sensitive. The incomplete clinical correlation weakens the primary olfactory theory unless it is proposed that IPD is primarily a genetic process, e.g. there might be an inherited neuronal defect that causes delayed onset of damage in the olfactory and motor systems. The olfactory defect might be the first to develop, and be ignored by patients (and clinicians). The disease would then come to light only when the extrapyramidal features emerged. (iii) Pathological. While we found Lewy bodies in every olfactory bulb from pathologically confirmed IPD cases, this may not be relevant aetiologically. Lewy bodies are widespread in the brain and even the enteric nervous system. The Lewy body is nonetheless considered to be the hallmark of IPD. On clinical and pathological grounds it cannot be said whether involvement of the olfactory system in PD is disproportionate compared to the strianigral system, nor whether the disease starts in the olfactory system. The severity of Lewy body formation in olfactory compared to non-olfactory areas is unknown. Preliminary information from α-synuclein expression in the rat suggests that the olfactory system is the site of major expression of this gene. If the olfactory vector theory is correct then there should be more Lewy bodies in the peripheral parts of the olfactory system compared to more central rhinencephalic areas, but there are no comparative data on this at present. We found most Lewy body damage in caudal (anterior olfactory nucleus) rather than rostral bulb structures, which is the reverse of what one would expect if the pathogen entered the CNS through the nose. Pathological evidence from Alzheimer’s disease suggests that the initial insult is central with peripheral spread. There is one recorded case of Alzheimer’s disease with an imperforate cribriform plate and a rudimentary olfactory system. Such arguments tend to destroy the olfactory vector theory, at least for Alzheimer’s disease where the nature of the olfactory defect may be similar to that of IPD. Our preliminary findings in AD suggest a different pattern of olfactory damage. While all our AD patients had abnormal UPSIT score, the OEP in the few tested so far was normal. This implies that the peripheral part of the olfactory system is relatively intact and complements the pathological data. In IPD, smell identification and OEP are abnormal.

A final point to consider is what we mean by a disease. The frequency of the three cardinal signs of PD is not well established, and was addressed only by Hoehn and Yahr at a time when parkinsonian syndromes were less well appreciated. No single sign is pathognomonic of PD. Akinesia is most consistent, but it is absent, for instance, in benign tremulous PD and on its own is not diagnostic. The absence of a precise clinical definition might be a reflection of our inadequate understanding of IPD. Defective smell sense is found in about 80% of IPD classified clinically. What if there were patients with tremor, rigidity and akinesia, of whom 80% were blind? Would this be classified as movement or visual disorder? If the blindness came first the disease would probably be classified as a visual disorder and it would then be proposed that the condition was a visual problem with motor accompaniments. If blindness is replaced by anosmia, the analogy is complete. The most disabling symptoms and signs (and indeed the initial symptoms and signs) do not necessarily equate with the primary causative mechanism.

In summary, evidence at clinical level shows profound impairment of smell function both subjectively (UPSIT) and objectively (OEP) in about 80% of hospital-based patients with IPD. There is unconfirmed insensitivity to pizza-like odor suggesting specific anosmia, which could be congenital or acquired. Pathological evidence shows Lewy body change throughout the olfactory pathway. New genetic information implies that α-synuclein is primarily an olfactory pathway gene with significant but less marked expression in extrapyramidal sites. The evidence of severe olfactory impairment in PD is overwhelming. It may be inferred therefore, that this is a primary phenomenon. Whether the damage starts in the olfactory pathways cannot be confirmed at present, but we suggest that it does.

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signs, disease stage or disease duration. Neurology 1988; 38:1237–44.


