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Olfactory Testing as an Aid in the Diagnosis of Parkinson's Disease: Development of Optimal Discrimination Criteria

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Since olfactory dysfunction is among the first signs of idiopathic Parkinson's disease (PD), olfactory testing may aid in the early 'preclinical' diagnosis of this disorder. Indeed, the proportion of early-stage PD patients with olfactory dysfunction appears to be greater than the proportion of early-stage PD patients exhibiting some of the cardinal signs of PD. Because olfactory function varies in the general population and declines with age, empirically-based criteria are needed by the clinician to establish whether the degree of olfactory loss observed in a given patient is concordant with the presence of PD. In this study, we present cutoff criteria for the optimal assessment of olfactory dysfunction in the evaluation of PD. Specifically, we present scores for the University of Pennsylvania Smell Identification Test (UPSIT) that best discriminate between PD patients and age-matched controls. Receiver operating characteristic (ROC) curves, based upon sensitivity and specificity estimates, were computed for three age groups (≤60 yrs, 61–70 yrs, and ≥71 yrs) and scores with highest sensitivity and specificity were determined. Sex- and age-related differences in the test scores were observed, with lower scores occurring for men and for the older patient groups.

Key words: diagnosis, olfaction, Parkinson's disease, Parkinsonism, smell, UPSIT

IDIOPATHIC PARKINSON'S DISEASE (PD) has been classically considered a motor system disease, its diagnosis being based upon the presence of a set or subset of cardinal motoric signs (e.g. rigidity, bradykinesia, tremor and postural reflex disturbance). Indeed, James Parkinson, in his 1817 monograph on shaking palsy (Parkinson, 1817), succinctly defined this disorder as 'Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: *the senses and intellects being uninjured*' (italics added).

It is now known that a number of sensory disturbances are present, in varying degrees, in persons with PD. These include changes in olfactory perception (for review, see Doty, 1991), visual contrast sensitivity (Bulens *et al.*, 1986), colour perception (Büttner *et al.*, 1993), perception of the visual vertical (Proctor *et al.*, 1964), and in sensations associated with proprioception and motor control (Snider & Sandyk, 1987). Unfortunately, most such alterations appear to be poor diagnostic markers of early PD, largely because of relatively low prevalence or their heterogeneity in presentation.

An apparent exception to this rule is olfactory dysfunction, which is reliably observed in early PD on a wide range of quantitative olfactory tests, including tests of odour identification, detection and discrimination. Doty, Deems & Stellar (1988), for example, found that 73 of 81 patients studied (90%) had odour identification test scores lower than their matched normal controls. The PD-related loss is bilateral (Doty *et al.*, 1992), present in early hemiparkinsonism (Doty *et al.*, 1988, 1992), stable over time (Doty *et al.*, 1988) and unrelated to disease stage (Doty *et al.*, 1988; Quinn, Rossor and Marsden, 1987; Ward, Hess & Calne, 1983), degree of motoric symptomatology (Doty *et al.*, 1989; Ward *et al.*, 1983) or use of antiparkinson medications (Doty *et al.*, 1988; Quinn *et al.*, 1987; Ward *et al.*, 1983). Importantly, among the

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major motor disorders, this alteration in ability to smell is relatively specific to PD. Thus, decreased ability to smell is absent, or present infrequently or only to a minor degree, in progressive supranuclear palsy (a condition which shares a number of signs with PD) (Doty *et al.*, 1993), essential tremor (Busenbark *et al.*, 1992), multiple system atrophy (Wenning *et al.*, 1993), amyotrophic lateral sclerosis (Sajjadian *et al.*, 1994), multiple sclerosis (Doty *et al.*, 1984) and parkinsonism induced by the proneurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Doty *et al.*, 1992). Additionally, subtle differences in olfactory dysfunction exist among subtypes of PD. For example, slightly greater dysfunction is present, on average, in patients with postural instability-gait predominant PD than with tremor-predominant PD (Stern *et al.*, 1994).

In the light of such observations, olfactory testing may aid in the clinical diagnosis of early-stage PD; indeed, decreased olfactory function might even be considered a primary sign or feature of PD. However, since such dysfunction is present to some degree in the general population and age-related declines in the ability to smell are well documented (Deems *et al.*, 1991; Doty *et al.*, 1984), empirically-based standards are needed by the clinician to determine whether the degree of olfactory loss in a given patient is concordant with that expected in PD. To this end, we established scores for the University of Pennsylvania Smell Identification Test (UPSIT; see Methods section) that optimally discriminate between PD patients and age-matched controls. As described in detail below, receiver operating characteristic (ROC) curves, based upon sensitivity and specificity estimates, were computed for three age groups chosen to take into account normal presbyosmia: ≤60 yrs, 61–70 yrs, and ≥71 yrs (Fletcher, Fletcher & Wagner, 1988). Those test scores which fell furthest from the positive diagonal of the ROC curves defined the optimal UPSIT cutoff points.

Methods

Subjects

The overall study group consisted of 180 PD patients and 612 controls, with four controls being matched to each PD patient in the ≤60 and ≥70 year old subject groups. Two or three controls were matched to each PD patient in the 61–69 year age category because fewer appropriate controls were available for such matching in this group. The matches were made on the basis of age and gender and, within the constraints of the matching procedure, were randomly selected from a database of over 2500 subjects maintained at the University of Pennsylvania Smell and Taste Center. This database includes individuals from the community at large who had been administered UPSIT (e.g. persons tested at fairs and public events, employees and students of the University of Pennsylvania, and healthy ambulatory residents of homes for the elderly). The PD patients were outpatients from the Department of Neurosurgery at St. Barnabas Medical Center, Livingston, New Jersey, the Department of Neurology, Graduate Hospital, Philadelphia, Pennsylvania, and the California Parkinson's Foundation, San Jose, California, and consisted primarily of subjects with early-stage PD [number of subjects at Hoehn and Yahr (1967) stages I–III = 102, 55 and 23, respectively]. At the time of testing, 31 of the patients were unmedicated (most were associated with the DATATOP program; see Parkinson Study Group, 1989), 137 were taking Sinemet or another dopaminergic agent (e.g. Amantadine) either alone or in conjunction with other PD medications (e.g. benztropine mesylate, deprenyl, trihexyphenidyl) and 23 were taking either deprenyl or trihexyphenidyl alone. The duration of the parkinsonian symptoms ranged from 3 months to 48 years (median = 5.0 yrs). All of the subjects scored 35 or better on the Picture Identification Test (a test analogous to the UPSIT except that pictures, rather than odours, are used as stimuli), precluding the possibility that low UPSIT scores were due to cognitive problems in test taking or to non-olfactory elements of the UPSIT (Vollmecke & Doty, 1985).

Olfactory testing

The UPSIT was the test instrument employed in this study. This standardized test (commercially available as the Smell Identification Test™, Sensonics, Inc., Haddon Heights NJ) is highly reliable (test-retest r's > 0.90) and correlates strongly with more traditional types of olfactory tests, including odour detection threshold tests (Doty, Shaman & Dann, 1984; Doty, Agrawal; & Frye, 1989). Procedurally, a subject is required to identify, in a 4-alternative multiple choice format, each of 40 odorants presented on microencapsulated 'scratch and sniff' labels. For example, one of the test items reads: 'This odour smells most like: (a) chocolate; (b) banana; (c) onion; or (d) fruit punch', and the subject is required to provide an answer even if no smell is perceived (i.e. the test is forced-choice). The number of items out of 40 that were answered correctly served as the dependent measure.

Development of receiver operating characteristic (ROC) curves

Sensitivity and specificity estimates were calculated for values at and below 32 of the 40 possible UPSIT scores (0, 5 and 10–40) (chance performance = 10). Sensitivity was defined as the proportion of PD patients falling at or below each of these cut-off scores, where values at or below each score were considered abnormal (sensitivity = true positives/(true positives + false negatives). Specificity was defined as the percent of control subjects who fell above each UPSIT cut-off score and therefore evidence a

'normal' test result (specificity = true negatives/(true negatives + false positives). In accord with standard practice, the ROC curves were calculated by plotting the sensitivity estimates vs. 1 minus the specificity estimates (Fletcher *et al.*, 1988). The ROC lines were fitted to the resulting data points using a LOWESS smoothing method (Cleveland, 1979, 1981), a procedure which does not presuppose the shape of the function and incorporates a locally weighted regression algorithm to obtain the best fit (Wilkinson, 1990).

Results

The ROC curves are presented in Fig. 1 for the males and females within each age group. Each data point represents one of the aforementioned UPSIT scores. Those UPSIT scores farthest away from the positive diagonal reflect optimization of the sensitivity and specificity estimates and, thus, test scores which best discriminate between PD and control subjects.

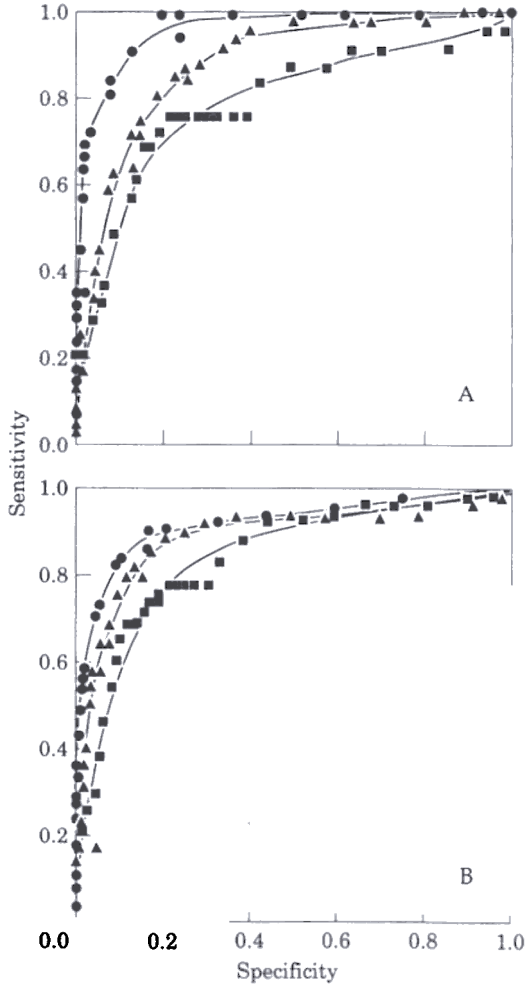

Figure 1. Receiver Operating Characterstic (ROC) curves relating sensitivity and specificity. (A) Males; (B) Females. Note gender and age group differences in functions. The most discriminative UPSIT scores are found in the upper left corners. Curves fitted using a LOWESS smoothing method (Wilkinson, 1990). ● ≥60 yrs; ▲ 61–70 yrs; ■ ≥71 yrs.

Table 1. Optimal cut-off values and associated sensitivity and specificity estimates determined from Receiver Operator characteristic (ROC) curves. M = Males Only; F = Females Only; Respective sample sizes for the PD and normal subject groups: ≤ 60 yrs: males, 32 & 128; females, 28 & 112; 61–70 yrs: males, 52 & 76; females, 20 & 104; ≤ 71 yrs: males, 25 & 100; females, 23 & 92

Age Group	Score		Sensitivity		Specificity	
	M	F	M	F	M	F
≤60 yrs	31	33	.91	.79	.88	.85
61–70 yrs	25	30	.81	.80	.82	.88
≥71 yrs	22	25	.76	.78	.78	.82

Note: Sensitivity = true positives/(true positives + false negatives)
Specificity = true negatives/(true negatives + false positives)

The most discriminatory test scores are presented in Table 1, along with corresponding sensitivity and specificity estimates. Note that these scores decrease as a function of age for each of the study groups and that, on average, lower UPSIT scores are needed to define PD-related pathology for the males than for the females. Thus, a clinician who evaluates a female patient 60 years of age or younger who has an UPSIT score of 33 or less can assume, with a reasonable degree of certainty, that this patient has an olfactory loss congruent with the loss expected in female patients with PD. On the other hand, if this patient were male, an analogous assumption would require an UPSIT score of 31 or less.

Discussion

In this study, we provide guidelines for the possible use of the UPSIT as an aid in the early diagnosis of PD; specifically, optimal cut-off values are defined for establishing whether the degree of olfactory dysfunction observed in a given patient is of a magnitude concordant with that expected in PD. The cut-off values listed in Table 1 will help the clinician to minimize his or her error in making this decision.

Since the PD subjects of our study were already identified as having PD, the sensitivity and specificity estimates we obtained cannot be viewed as comparable to classical sensitivity and specificity

estimates obtained by epidemiologists. To estimate the sensitivity and specificity of UPSIT for detecting either early clinical or 'preclinical' PD in the general population, large numbers of subjects, not yet identified as having or not having PD, would need to be evaluated prospectively and then followed longitudinally to determine what proportion ultimately develop PD.

Olfactory dysfunction, relative to other clinical signs of PD, is unique on several grounds and, thus, may add an important independent dimension to the PD diagnostic process. This uniqueness stems not only from the fact that such dysfunction is sensory, rather than motor, but that it (a) is prevalent to a relatively high degree in the earliest stages of the disease process, (b) does not evidence longitudinal progression, (c) is unrelated to the use of antiparkinsonian medications, (d) does not differ during the 'on' and 'off' states of patients with severe motor fluctuations who are on l-dopa therapy, and (e) is unrelated in magnitude to the degree of motoric or cognitive symptomatology (implying independence from the more dynamic elements of the disease proper) (see opening paragraphs for references).

Although the basis for PD-related olfactory loss is unknown, its early presentation and lack of progression with the disease process are compatible with the hypothesis that it may reflect the adverse effects of an environmental toxin or other agent which enters the brain via the olfactory epithelium (Doty, 1991). Olfactory receptor cells serve as a primary means of entry into the central nervous system for a number of viruses and macromolecules which, in animal models, can damage olfactory neurons (e.g. Barthold, 1988; Lundh, Kristensson & Norrby, 1987; Monath, Croop & Harrison, 1983; Moarles *et al.*, 1988; Stroop, 1995). Importantly, the blood-brain barrier is largely compromised in this region, although the olfactory mucosa contains very high concentrations of enzymes that metabolize xenobiotics (e.g. cytochromes P-450, flavin containing monooxygenase and aldehyde dehyrogenases, and carboxylesterases) (Dahl, 1985a,b,c, 1988). Interestingly, the metabolic rates for xenobiotics within nasal tissue typically exceed those of other extrahepatic tissues and commonly exceed those of the liver (Dahl, 1984).

Whatever its basis, olfactory dysfunction appears to be an excellent marker for idiopathic PD. Hopefully, the present study will encourage neurologists and others to more fully explore the usefulness of olfactory testing in the early or 'preclinical' diagnosis of PD.

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References

Ansari KA, Johnson A (1975) Olfactory function in patients with Parkinson's disease. J Chron Dis 28:493–497

Barthold SW (1988) Olfactory neural pathway in mouse hepatitis virus nasoencephalitis Acta Neuropathol 76:502–506

Bulens C, Meerwaldt JD, van der Wildt GJ, Keemink CJ (1986) Contrast sensitivity in Parkinson's disease. Neurology 36:1121–1125

Busenbark KL, Huber SJ, Greer G, Pahwa R, Koller WC (1992) Olfaction function in essential tremor. Neurology 42:1631–1632

Büttner Th, Kuhn W, Klotz P, Steinberg R, Voss L, Bulgaru D, Przuntek H (1993) Disturbance of colour perception in Parkinson's disease. J Neural Transm [P-D Sect] 6:11–15

Cleveland WS (1979) Robust locally weighted regression and smoothing scatterplots. J Amer Stat Assoc 74:829–836

Cleveland WS (1981) LOWESS: A program for smoothing scatterplots by robust locally weighted regression. Amer Statistician 38:261–269

Dahl AR (1985a) Activation of carcinogens and other xenobiotics by nasal cytochromes P-450. In AR Boobis, J Caldwell, F DeMatteis, CR Elcombe (eds) Microsomes and Drug Oxidations. Philadelphia: Taylor and Francis, pp 299–309

Dahl AR (1985b) Possible consequences of cytochrome P-450-dependent monooxygenases in nasal tissues. In CS Borrow (ed) Toxicology of the Nose. Research Triangle Park, NC: Chemical Industry Institute for Toxicology, pp 263–271

Dahl AR (1985c) Selective activation of carcinogens and other toxicants by nasal mucosae. In W Paton, J Mitchell, P Turnder (eds) Proceedings of the Ninth IUPHAR Congress of Pharamacology, Vol 1. London: Macmillan, pp 203–208

Dahl AR (1988) The effect of cytochrome P-450-dependent metabolism and other enzyme activities on olfaction. In FL Margolis, TV Getchell (eds) Molecular Neurobiology of the Olfactory System. New York: Plenum Press, pp 51–70

Deems, DA, Doty RL, Settle RG, Moore-Gillon V, Shaman P, Mester AF, Kimmelman CP, Brightman VJ, Snow JB Jr (1991) Smell and taste disorders: A study of 750 patients from the University of Pennsylvania Smell and Taste Center (1981–1986) Arch Otolaryngol Head Neck Surg 177:519–528

Doty RL (1991) Olfactory dysfunction in neurodegenerative disorders. In TV Getchell, RL Doty, LM Bartoshuk & JB Snow Jr (eds), Smell and Taste in Health and Disease. New York, Raven, pp 735–751

Doty RL, Agrawal U, Frye RE (1989) Evaluation of the internal consistency reliability of the fractionated and whole University of Pennsylvania Smell Identification Test (UPSIT). Percept Psychophys 45:381–384

Doty RL, Deems D, Stellar S (1988) Olfactory dysfunction in Parkinson's disease: A general deficit unrelated to neurologic signs, disease stage, or disease duration. Neurology 38:1237–1244

Doty RL, Golbe LI, McKeown DA, Stern MB, Lehrach CM, Crawford D (1993) Olfactory testing differentiates between progressive supranuclear palsy and idiopathic Parkinson's disease. Neurology 43:962–965

Doty RL, Riklan M, Deems DA, Reynolds C, Stellar S (1989) The olfactory and cognitive deficits of Parkinson's disease: Evidence for independence. Ann Neurol 25:166–171

Doty RL, Shaman P, Applebaum SL, Giberson R, Sikorsky L, Rosenberg L (1984) Smell identification ability: Changes with age. Science 266:1441–1443

Doty RL, Singh A, Tetrud J, Langston JW (1992) Lack of olfactory dysfunction in MPTP-induced parkinsonism. Ann Neurol 32:97–100

Doty RL, Stern MB, Pfeiffer C, Gollomp SM, Hurtig HI (1992) Bilateral olfactory dysfunction in early stage treated and untreated idiopathic Parkinson's disease. J Neurol Neursurg Psychiat 55: 138–142

Fletcher RH, Fletcher SW, Wagner EH, (eds) (1988) Clinical Epidemiology. 2nd Edition. Baltimore: Williams & Wilkins

Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression, and mortality. Neurology 17:427–442

Lundh B, Kristensson K, Norrby E (1987) Selective infections of olfactory and respiratory epithelium by vesicular stomatitis and sendai viruses. Neuropathol Appl Neurobiol 13:111–122

Monath TP, Croop CB, Harrison AK (1983) Mode of entry of a neurotropic arbovirus into the central nervous system: Reinvestigation of an old controversy. Lab Invest 48:399–410

Morales JA, Herzog S, Kompter C, Frese K, Rott R (1988) Axonal transport of Borna disease virus along olfactory pathways in spontaneously and experimentally infected rats. Med Microbiol Immunol 177:51–68

Parkinson Study Group (1989) Effect of deprenyl on the progression of disability in early Parkinson's disease. New Engl J Med 321:1364–1371

Proctor F, Riklan M, Cooper IS, Teuber HL (1964) Judgment of visual and postural vertical by parkinsonian patients. Neurology 14:287–293

Quinn NP, Rossor MN, Marsden CD (1987) Olfactory threshold in Parkinson's disease. J Neurol Neurosurg Psychiat 50:88–89

Sajjadian A, Doty RL, Gutnick DN, Shirugi RJ, Sivak M, Perl D (1994) Olfactory dysfunction in amyotrophic lateral sclerosis. Neurodegeneration 3:1–5

Snider SR, Sandyk R (1987) Sensory dysfunction. In WC Koller (ed), Handbook of Parkinson's disease. New York: Marcel Dekker, Inc, pp 171–180

Stern MB, Doty RL, Dotti M, Corcoran P, Crawford D, McKeown DA, Adler C, Gollomp S, Hurtig H (1994) Olfactory function in Parkinson's disease subtypes. Neurology 44:266–268

Stroop WG (1995) Viruses and the olfactory system. In RL Doty (ed) Handbook of Olfaction and Gustation. NY: Marcel Dekker, pp 367–397

Vollmecke TA, Doty RL (1985) Development of the Picture Identification Test (PIT): A research companion to the University of Pennsylvania Smell Identification Test. Chem Senses 10:413–414

Ward CD, Hess WA, Calne DB (1983) Olfactory impairment in Parkinson's disease. Neurology 33:943–946

Wenning GK, Shephard B, Magalhaes M, Hawkes CH, Quinn NP (1993) Olfactory function in multiple system atrophy. Neurodegeneration 2:169–171

Wilkinson L (1990) SYGRAPH: The System for Graphics. Evanston, IL: SYSTAT, Inc.