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# Hyposmia in Progressive Supranuclear Palsy

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**Abstract:** Previous studies suggested that olfaction is normal in progressive supranuclear palsy (PSP). We applied the University of Pennsylvania Smell Identification Test (UPSIT) to 36 patients with PSP who scored more than 18 on the Mini Mental State Examination (MMSE), 140 patients with nondemented Parkinson's disease (PD) and 126 controls. Mean UPSIT scores in PSP were lower than in controls ($P < 0.001$) but higher than in PD ($P < 0.001$) after adjusting for age, gender, and smoking history. For patients with PSP, UPSIT scores correlated with MMSE ($r = 0.44$, $P = 0.006$) but not disease duration ($P = 0.6$), motor subscale of the Unified Parkinson's Disease Rating Scale ($P = 0.2$), or Frontal Assessment Battery ($P = 0.5$). The brains of six of the patients with PSP were examined postmortem and all revealed neurofibrillary tangles and tau accumulation in the rhinencephalon, although only three had hyposmia. Further prospective studies including patients with early PSP and PSP-P with postmortem confirmation might help clarify if smell tests could be useful when the differential diagnosis lies between PD and PSP. © 2010 Movement Disorder Society

**Key words:** Parkinson's disease; postmortem analysis; UPSIT; smell; olfaction

The classic clinical features of Progressive Supranuclear Palsy (PSP) include supranuclear vertical ophthalmoplegia, severe postural instability with early falls,[1,2] and subcortical dementia[3] most commonly developing in the seventh decade of life. PSP shares many common features with Parkinson's disease (PD)[4,5] but previous studies have suggested that hyposmia, which is a common and early feature of PD,[6,7] is not present in PSP. In a study by Wenning et al.[8] 15 patients with PSP and 123 controls scored significantly higher on an odor identification test than did 118 patients with PD. In another publication by Doty et al.,[9] 21 patients with PSP performed significantly better than 21 PD and nonsignificantly worse than did 21 controls. Muller et al.[10] smell tested a series of parkinsonian patients including one with clinical PSP; this patient was found to be hyposmic. The numbers of patients with PSP in each of these studies were relatively small and no attempt was made to correlate smell test performance in the patients with PSP with cognitive performance. Pathological confirmation of the diagnosis of PSP was also not available.

We have administered the UPSIT to 36 patients with PSP and compared the findings with control and patients with PD. We tried to correlate smell test scores with results of bedside testing of cognitive and

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motor function, and in the 6 patients who underwent postmortem examination, a detailed examination of the rhinencephalon was performed.

## PATIENTS AND METHODS

### Clinical Studies

#### Subjects

*Thirty-six patients with PSP (20 men and 16 women)* were recruited from the movement disorders specialist clinics at the National Hospital for Neurology and Neurosurgery, Queen Square London (n = 25), The Regional Neuroscience Centre Newcastle upon Tyne (n = 7), and The Royal Gwent Hospital (n = 4) from January 2003 to February 2008. Twenty-five patients fulfilled NINDS-SPSP criteria for the diagnosis of probable PSP[11]; 33 of 36 patients had a supranuclear vertical gaze palsy (SNGP) at the time of assessment, the remaining 3 patients had presented with falls within less than a year of symptom onset: 2 had slowing of vertical saccades (fulfilling criteria for possible PSP) and 1 had limitation of upgaze but normal downgaze, but was diagnosed as definite PSP at postmortem. Nine of 36 had a history of ever smoking. Mean age of the subjects was 69.2 years (SD = 6.3 years, range 56–82 years) and mean duration of symptoms was 4.8 years (SD = 2.7 years, range 1.2–12.6 years). All subjects scored more than 18/30 in the Mini Mental State Examination (MMSE) testing[12] and 2 of 2 in the naming component of this test; mean MMSE score was 25.7 (SD = 3.2, range 19–30). Subjects also performed the Frontal Assessment Battery (FAB) which is a bedside test of executive function that evaluates conceptualization and abstract reasoning, mental flexibility, motor programming and executive control of action, resistance to interference, self-regulation, inhibitory control, and environmental autonomy.[13] Mean score in the FAB for the 32 patients assessed was 11.2 (SD = 3.1, range 4–16). Twenty-seven of the patients with PSP performed the Unified Parkinson's Disease Rating Scale Part III[14] (UPDRS III), which has been validated for PSP,[15] with a mean score of 27.1 (SD = 10.9, range 12–46). At the time of examination, 13 patients were taking levodopa preparations and 17 amantadine. All but 1 patient had recurrent falls and 12 had suffered bone fractures; participants were excluded if they had a previous history of head trauma leading to loss of consciousness.

*One hundred and forty patients* with *PD* (83 men and 57 women) fulfilling the Queen Square Brain Bank criteria for PD[16] were recruited from the movement disorders specialist clinics at the National Hospital for Neurology and Neurosurgery Queen Square from April 2005 to February 2008. Seventy of 140 had a history of ever smoking. Mean age was 65.6 years (SD = 11.4 years, range 27–86 years) and mean duration of symptoms was 10.4 years (SD = 6.4 years, range 0.5–30 years). Mean MMSE score for the 108 patients with PD who underwent the test was 29.0 (SD = 1.1, range 27–30). Mean UPDRS III score in 92 patients assessed was 27.1 (SD = 10.3, range 8–58). *One hundred and twenty-six control subjects* (63 men and 63 women) were recruited among staff, visitors and patients from non-neurological departments of the same hospitals. None had a history of chronic neurological or psychiatric disorder, or previous history of head trauma leading to loss of consciousness; 59/126 had a previous or current history of smoking; mean age was 59.6 years (SD = 12.9 years, range 27–90 years).

All PD and control subjects were screened for dementia using the first item of the Part I of the Unified Parkinson's Disease Rating Scale[14]; those who scored ≥1 underwent Mini Mental State Examination (MMSE)[12]; if the score in the MMSE was lower than 27, the subject was excluded from the research. Consent was obtained from all participants and the protocol was approved by the local ethics committee of the relevant institutions.

#### Smell Testing

All subjects were tested with the 40-item University of Pennsylvania Smell Identification Test (UPSIT), American-English version.[17] This 40-item scratch and sniff test can be self-administered, but the patients had the help of the examiner or a carer when mobility or blepharospasm precluded scratching the booklets, or reading and marking response options.

#### Statistical Analysis

The UPSIT score in the three groups of patients was compared using a multiple linear regression analysis using the UPSIT score as the dependent variable and age, gender, smoking habit, and group (two indicator variables were used to compare PD and control with PSP as the reference group) as predictors. The same procedure was performed including only the 17 patients with PSP who scored 27 or more in the MMSE, and all the PD and control subjects. In this subgroup, 7 (41.2%) subjects were women and 4 (23.5%) had a positive history of smoking; mean age was 69.8 years (SD = 6.6, range 60.6–82.4 years), mean disease

duration was 4.9 years (SD = 3.2, range 1.2–12.6 years), and mean MMSE was 28.3 (SD = 0.9, range 27–30).

To study the association of the smell score with other clinical features in the patients with PSP, we used univariate regression analyses with the UPSIT as outcome variable and as covariates each of the clinical data variables (disease duration, medication usage, fulfillment of NINDS-SPSP criteria for probable PSP, and scores in the UPDRS III, MMSE, and FAB) always in addition to age, gender, and smoking. Assumptions for the regression analyses were checked by the analyses of the residuals.[18] A significance level of 0.05 was used throughout.

A receiver operating characteristic (ROC) curve was constructed to demonstrate how sensitivity and specificity varied according to the cut-off value chosen in the UPSIT, when differentiating between 36 PSP from 86 PD of similar age, gender, and smoking history (age in the two groups was compared using independent samples *t*-test, and gender and history of smoking using $\chi^2$).

## Pathological Studies

### Subjects

We examined the brains of 6 of the patients with PSP who had consented for brain donation to the Queen Square Brain Bank (QSBB) for Neurological Disorders, UCL Institute of Neurology, UCL, London, UK. Consent was obtained using a protocol approved by a Multicentre Research Ethics Committee and the tissue is stored at the QSBB under a full license from the UK Human Tissue Authority. Two patients with PSP died from aspiration pneumonia, two from sepsis, one from urinary tract infection, and one from complications related to bedsores.

### Pathological Diagnosis of Neurodegenerative Processes

All 6 patients were diagnosed as PSP according to the National Institute for Neurological Diseases and Stroke-Society for PSP (NINDS-SPSP) criteria.[19] Neuropathological data were obtained including analysis of neuritic plaque density estimated according to The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria,[20] Braak and Braak staging of neurofibrillary tangle pathology determined using tau immunohistochemistry,[21] and α-synuclein Braak staging according to screening of regions of vulnerability using α-synuclein immunohistochemistry[22]; cases in which no α-synuclein related pathology was found in any of the areas screened received a Braak stage score of "zero."

### Evaluation of the Rhinencephalon

Sections of 8 and 13 μm from formalin-fixed wax-embedded blocks of the mesial temporal cortex and forebrain were cut in all subjects, but the olfactory tract was only available for examination in two. The 13 μm sections were stained with Luxol fast blue/cresyl violet for the delimitation of the areas of interest using established anatomical guidelines[23,24] which included the olfactory tract, anterior olfactory nucleus, frontal and temporal segments of the piriform cortex, and anterior cortical nucleus of the amygdala and periamygdaloid cortex. Adjacent 8 μm sections were used for immunohistochemistry with a monoclonal antibody to α-syn (Novocastra, Newcastle upon Tyne, UK; 1:75), tau (AT8 antibody, Thermo Scientific, Loughborough, UK; 1:200), and the 3R (RD3) and 4R (RD4) tau-specific monoclonal antibodies[25] (Upstate/Millipore, Dundee, UK; RD3, 1:3,000; RD4, 1:100). The severity of Lewy body and Lewy neurite pathology was graded in each of the areas separately following the criteria proposed by McKeith et al.[26] for semiquantitative grading of lesion density in a zero to four scale as previously described.[27] Severity of tau-related pathology was graded according to procedures that are routine in our laboratory.[4]

# RESULTS

## Clinical Studies

Upon specific questioning, 9.7% of controls, 20% of PSP and 57% of PD patients reported smell problems. Mean UPSIT score was higher in PSP than PD [$P < 0.001$, 95% confidence interval (CI) for $\beta = -2.9$ to $-7.0$, PSP as reference group] and lower in PSP than in the control group ($P < 0.001$, 95% CI for $\beta = +3.7$ to $+8.1$, PSP as reference group) after adjusting for the independent predictors age ($P < 0.001$, 95% CI for $\beta = -0.12$ to $-0.24$), gender ($P = 0.008$, 95% CI for $\beta = -0.46$ to $-3.1$, women as reference group) and positive history of smoking ($P = 0.03$, 95% CI for $\beta = -0.15$ to $-2.8$, no history of smoking as reference group). Figure 1A shows a box plot of UPSIT results in the three groups. The multiple linear regression analysis including all PD and control subjects and only the subset of 17 patients with PSP with MMSE scores of 27 or higher also demonstrated the UPSIT score was higher in PSP than PD ($P < 0.001$, 95% CI for $\beta = -4.6$ to $-10.3$, PSP as reference group) and lower in PSP than in the control group ($P < 0.024$, 95% CI for $\beta = +0.4$ to $+6.3$, PSP as reference group) after adjusting for the independent predictors age ($P < 0.001$), gender ($P = 0.004$) and positive his-

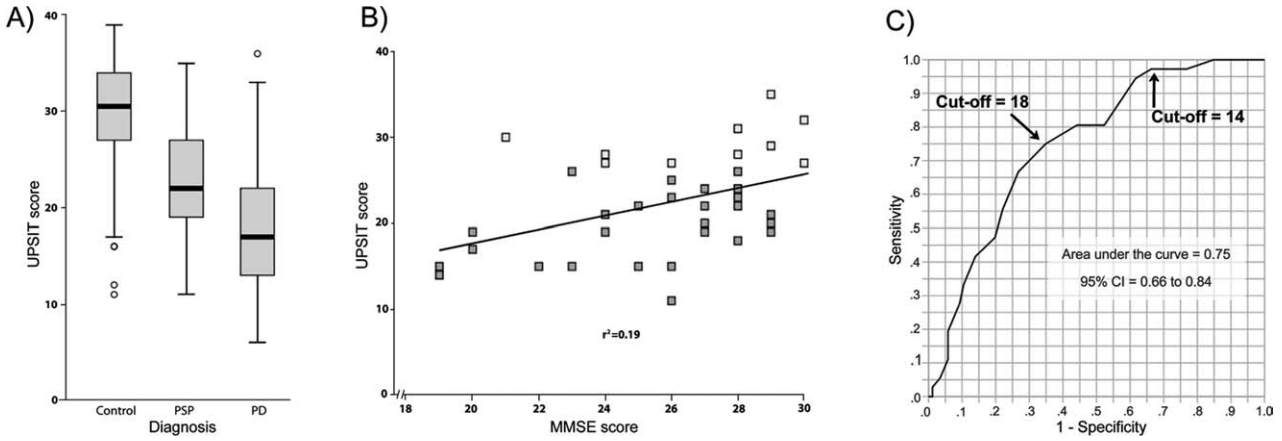


**FIG. 1.** Results of the clinical experiment. **A**: Box plot of the UPSIT score in the three patient groups. The median (the horizontal line) is within the box containing the central 50% of the observations and the error bar contains the central 95% of the ordered observations. Outliers are showed as circles. **B**: Scatter plot of UPSIT and MMSE scores in the PSP group. UPSIT scores bellow the 25 percentile for the control group are filled in dark grey. **C**: Receiver operating characteristic (ROC) curve showing that a cut-off of 18 gives the best balance between sensitivity and specificity (75.0% and 65.1%, respectively), whereas a cut-off of 14 provides 97.3% sensitivity at the expense of a low specificity. UPSIT, 40-item University of Pennsylvania Smell Identification Test; MMSE, Mini Mental State Examination.

tory of smoking ($P = 0.03$). The Supplementary Information figure displays a box plot of the UPSIT in this group compared with the PD and control groups.

In the PSP group, only MMSE scores were significant predictors of the UPSIT ($P = 0.005$, 95% CI for $\beta = 0.27$–$1.41$). FAB ($P = 0.48$), disease duration ($P = 0.8$), fulfillment of NINDS-SPSP criteria for probable PSP ($P = 0.4$), current use of amantadine ($P = 0.9$), and UPDRS III scores ($P = 0.13$) were not independent predictors of the UPSIT score and age, gender, and smoking were not independent predictors in any of the regressions in the PSP group ($P > 0.05$ for all). Figure 1B displays a scatter plot of the UPSIT scores by the MMSE scores in PSP with the data labeled according to the classification of the UPSIT score in below or above the 25% for controls.

Figure 1C displays the ROC for the UPSIT differentiating 36 patients with PSP from 86 patients with PD. Patients in both groups were similar in age (95% CI mean age = 67.4–71.7 years for PSP, and 67.2–71.2 years for PD, *t*-test $P = 0.8$), gender distribution (percentage of women = 44.2% for PSP and 43.2% for PD, $\chi^2$ $P = 0.9$), and history of smoking (27.0% of the PSP and 27.9% of the PD subjects had history of current or previous smoking, $\chi^2$ $P > 0.99$). The best combination for accuracy measures was sensitivity 75.0% (95% CI = 58.7%–86.4%) and specificity 65.1% (95% CI = 54.6%–74.4%).

### Pathological Studies

Neurofibrillary degeneration with tau immunoreactivity of mild to moderate severity was found in the rhinencephalon of all 6 cases despite the fact that only three had had abnormal smell tests during life. Two of the patients with PSP had concomitant α-synuclein related pathology (one was classified as Braak Stage 2 and the other Braak Stage 3) with verifiable Lewy bodies and Lewy neurites in the olfactory structures, but only one of these had hyposmia. Figure 2 shows representative photomicrographs demonstrating tau and α-synuclein pathology in the rhinencephalon in one of the PSP cases. Detailed results of the postmortem examination in six PSP cases, together with the clinical findings in life and the smell test results are presented in Table 1.

## DISCUSSION

Our study confirms that the olfactory function of patients with PSP is significantly better than that found in patients with PD, but in contrast to two previous publications, it also shows that it is significantly reduced when compared with controls. In the 3 cases examined pathologically, tau accumulation was found in the rhinencephalon of all, even though three had normal olfaction on UPSIT testing.

The difference in our findings to those previously reported might be explained by the larger number of patients with PSP and the fact that we did not exclude patients with PSP who presented with cognitive impairment as long as they were deemed able to understand and collaborate with the test. Wenning et al.[8] excluded all demented patients based on DSM III criteria and Doty et al.[9] applied the Picture Identification Test (PIT) as a screen excluding those who

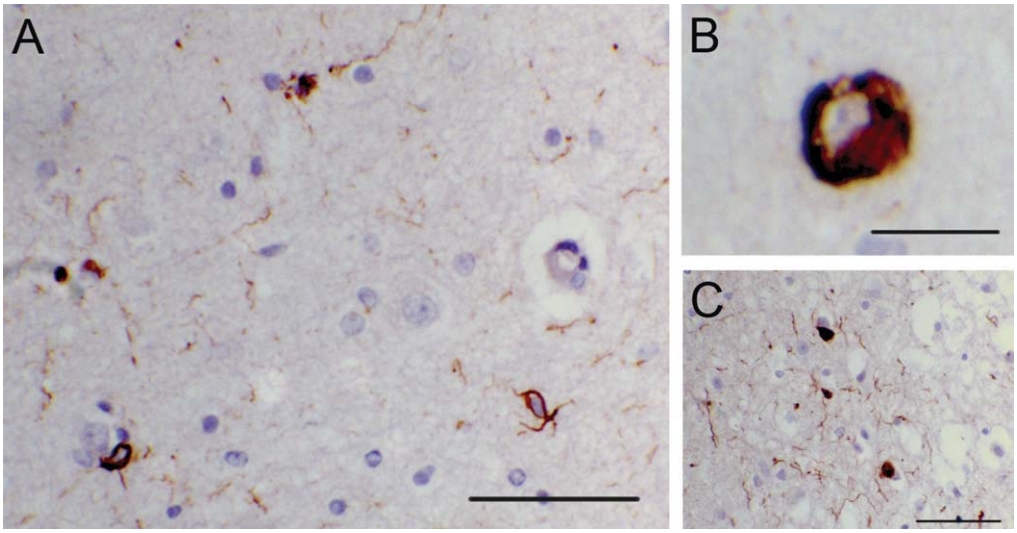


**FIG. 2.** Piriform cortex in a patient with PSP. Photomicrographs of the piriform cortex of patient PSP 3 stained with tau AT8 immunohistochemistry (Ser202/Thr205; 1:200) showing (**A**) typical PSP-type pathology, bar = 50 μm and (**B**) magnification of neurofibrillary tangle, bar = 20 μm; (**C**) α-synuclein immunohistochemistry (Novocastra; 1:75) showing Lewy-type pathology, scale bar = 50 μm.

scored less than 35 of 40. The PIT test was used to detect if subjects were able to recognize from pictures the 40 items of the UPSIT, but it is not a sensitive marker for cognitive deficits in PSP, which are better screened for by the FAB.[28] It is unlikely, however, that cognitive deficit fully explains the low UPSIT scores in our patients: all subjects scored 19 or more on the MMSE and were able to understand and collaborate with the identification task; the $r^2$ for the correlation between MMSE and UPSIT was 0.18, indicating that the MMSE variation explained only about 20% of the linear variation in the UPSIT. Two thirds of the patients with PSP with MMSE scores equal to or higher than 27 still presented with smell test scores below the 25th percentile for controls (see Fig. 1B) and of the 3 hyposmic patients with definite PSP confirmed at postmortem, two had normal MMSE and FAB scores when smell tested. Furthermore, a repeated regression analysis including only the PSP subjects who scored 27 or more in the MMSE confirmed that UPSIT scores were lower in the PSP than in the control group. No previous study in PSP investigated the relationship between MMSE and UPSIT, and there is no consensus in the literature regarding a minimum MMSE value that would allow reliable application of the UPSIT. This is partially due to the fact that subjects with Alzheimer's disease (AD) and dementia with Lewy bodies (DLB), two common causes of dementia both have hyposmia[29] and pathological changes in the rhinencephalon.[30]

Hyposmia is a common feature of tauopathies. Patients with AD present with tau pathology in the rhinencephalon, and PD and AD have a similar severity of hyposmia[29]; patients with Down's syndrome present with abnormal odor detection thresholds,[31] odor identification,[32,33] and abnormal olfactory event related potentials[34]; a previous study also showed hyposmia in the parkinsonism-dementia complex of Guam.[35] Corticobasal degeneration (CBD) is another tauopathy which may present with bradykinesia and there are clinical overlap syndromes which may be misdiagnosed as PSP. Luzzi smell tested 7 patients with CBD using an adapted battery and although some smell deficit was found, concluded that it was mild and most likely due to executive dysfunction[36]; Wenning smell tested 7 patients with CBD and found their UPSIT-40 result to be nonsignificantly different from controls[8]; Muller applied the Sniffin' Sticks battery to 2 patients and found them to have normal results.[37] A more recent and larger study using the UPSIT-40 and including 25 patients with corticobasal syndrome[38] demonstrated that only 8 had normal olfaction, whereas 8 had anosmia or severe hyposmia and the other 9 had mild or moderate hyposmia.

Tsuboi et al.[30] found tau accumulation in the olfactory bulb of 9 of 27 PSP cases. Some degree of PSP-type pathology was also present in the rhinencephalon of all our 6 patients. The fact that three of them had normal smell tests during life, suggests a poor clinicopathological correlation between tau-pathology in the rhinencephalon and in-vivo hyposmia. The relevance of pathological inclusions in the olfactory bulb, olfactory tract, and piriform cortex to the pathogenesis of

**TABLE 1.** *Definite cases of PSP included in the study*

| Case | PSP 1 | PSP 2 | PSP 3 | PSP 4 | PSP 5 | PSP 6 |
|---|---|---|---|---|---|---|
| Age (yr), sex | 61, men | 76, men | 75, men | 63, men | 65, men | 76, men |
| Smoking history | Negative | Negative | Negative | Ex-smoker | Negative | Ex-smoker |
| NINDS-SPSP[11] | Probable PSP | | Possible PSP | Probable PSP | Probable PSP | Probable PSP |
| Onset: age (yr), symptom | 60, gait disturbance | 73, falls | 71, personality change | 60, slurred speech | 60, falls | 70, falls |
| Disease duration (yr) | 1.5 | 2.6 | 4.0 | 3.2 | 3 | 6.5 |
| EOM | Classical SNGP | Limited upgaze | Classical SNGP | Classical SNGP | Classical SNGP | Classical SNGP |
| Levodopa response | Moderate | Moderate | None | Mild | Moderate | None |
| MMSE, FAB | 28/30, 16/18 | 29/30, 16/18 | 28/30, 8/18 | 26/30, n.a. | 29/30, 14/18 | 19/30, 4/18 |
| UPDRS Part III[14] | 24 | 30 | n.a. | 28 | n.a. | 45 |
| Time between smell test and death (yr) | 1.0 | 0.8 | 1.4 | 4.8 | 4.5 | <0.1 |
| Final diagnosis | PSP | PSP | PSP | PSP | PSP | PSP |
| Neurofibrillary pathology Braak and Braak stage[21] | II | II | II | II | II | II |
| α-Synuclein pathology Braak stage[22] | Stage "zero" | Stage 3 | Stage 2 | Stage "zero"[a] | Stage "zero" | Stage "zero" |
| Other diagnoses | Mild SAH, aneurysm | | Organized SDH | | Moderate small vessel disease | Argyrophilic grain disease |
| Olfactory α-synuclein pathology grade (McKeith et al.)[26] | None (PiF examined) | Grade 3 (PiF), none in PAC | Grade 2 (PAC), grade 3 (PIF, PIT) | None (PiF, PiT, PAC examined) | None (PiF, PiT, AON, OT examined) | None (PiT, PiT, AON, OT examined) |
| Olfactory PSP-type pathology (Williams et al.)[4] | Grade 1 (PiF) | Grade 1 (PiF) | grade 2 (PAC, PiF, PiT) | Grade 1 (PAC), grade 2 (PiF, PiT) | Grade 1 (PiT, AON, OT), grade 2 (PiF) | GRADE1 (AON, OT), grade 3 (PiF, PiT) |
| UPSIT | 22/40 | 20/40 | 31/40 | 27/40 | 26/30 (unfinished) | 15/40 |

AON, anterior olfactory nucleus; Braak stage, α-synuclein related pathology staging; EOM, extraocular movements; FAB, frontal assessment battery; MMSE, mini mental state examination; NINDS-SPSP, National Institute of Neurological Disorders and Stroke and the Society for PSP research criteria for the diagnosis of PSP; PAC, anterior cortical nucleus of the amygdala and periamygdaloid cortex; PiF and PiT, frontal and temporal divisions of the piriform cortex; OT, olfactory tract; PSP, progressive supranuclear palsy; SAH, subarachnoid hemorrhage; SDH, subdural haematoma; SNGP, supranuclear gaze palsy; UPDRS, Part III of the unified Parkinson's disease rating scale; UPSIT, University of Pennsylvania Smell Identification Test.

[a]Incomplete lower brainstem structures available.

hyposmia in PD is unknown; despite evidence that the olfactory bulb has some Lewy body pathology in virtually all patients with PD,[22,39] 10–30% of patients with PD who have been smell tested in various studies have normal olfaction. Furthermore, no prospective studies exist in which in-vivo smell tests were correlated with pathology either in the olfactory bulb, tract, or piriform cortex in PD. It is also possible that the time lapse between the smell test and the autopsy (1.4 years in one, and more than 4 years in the other two) resulted in additional pathological damage to the rhinencephalon, and had these patients been smell tested closer to the time of death, the smell tests might have been abnormal. In one of our patients with a clear hyposmic score, the postmortem revealed the coexistence of Lewy body pathology (Braak Stage 3, including the olfactory areas). Another patient also had concomitant Lewy body pathology (Braak Stage 2, including the rhinencephalon) but had a normal score; the time lapse to autopsy in this case was 1.4 years, and this patient also had an incidental finding of an organized subdural hematoma at autopsy.

It has been suggested smell tests might help differentiate PSP from PD. The accuracy of such differentiation in our sample (sensitivity 75.0% and specificity 65.1%) is poorer than that of smell tests in differentiating patients with PD from controls in the United Kingdom, where the UPSIT has sensitivity of 85.0% (95% CI 78.8%–89.7%) and specificity of 84.6% (95% CI 77.3%–89.9%).[40] In practical terms, a subject with an UPSIT score lower than 14/40 (a cut-off that provides a sensitivity of 97.3%) is unlikely to have PSP as opposed to PD (see Fig. 1C). To exclude patient with PSP who have cognitive impairment seems to us artificial in a disorder characterized by dysexecutive problems and problems with recall. A counsel of perfection would be to perform a full otolaryngological evaluation to exclude secondary causes of hyposmia in all subjects; although likely to increase the power of the study, such evaluations are impractical in routine neurology clinics where parkinsonian patients are seen.

Our data suggests that the UPSIT may not be a useful tool in routine neurological practice when attempting to distinguish PD and PSP although as a generalization smell sense is better preserved in PSP than PD. It is possible, however, that hyposmia may not occur in PSP-P (PSP-parkinsonism), an atypical clinical presentation of PSP-type tauopathy which presents with less cognitive decline[4,41] and is more likely to be confused with PD. These cases were excluded from this study because of the difficulty in accurate clinical diagnosis. Smell testing in early atypical parkinsonism combined with prospective follow-up and postmortem confirmation might provide supplementary information regarding the use of smell tests in the differential diagnosis of atypical Parkinsonism. Further studies of the rhinencephalon in PSP are also warranted to further clarify the link between PSP and hyposmia.

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