



Olfaction in patients with suspected Parkinsonism and scans without evidence of dopaminergic deficit (SWEDDs)

Laura Silveira-Moriyama, Petra Schwingenschuh, Angela O'Donnell, Susanne A Schneider, Pablo Mir, Fatima Carrillo, Carmen Terranova, Aviva Petrie, Donald Grosset, Niall Quinn, et al.

► To cite this version:

Laura Silveira-Moriyama, Petra Schwingenschuh, Angela O'Donnell, Susanne A Schneider, Pablo Mir, et al.. Olfaction in patients with suspected Parkinsonism and scans without evidence of dopaminergic deficit (SWEDDs). *Journal of Neurology, Neurosurgery and Psychiatry*, 2009, 80 (7), pp.744. 10.1136/jnnp.2009.172825 . hal-00552769

HAL Id: hal-00552769

<https://hal.science/hal-00552769>

Submitted on 6 Jan 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

TITLE: Olfaction in patients with suspected Parkinsonism and scans without evidence of dopaminergic deficit (SWEDDs)

CORRESPONDING AUTHOR: Prof. Andrew Lees, Reta Lila Weston Institute of Neurological Studies, UCL Institute of Neurology, 1 Wakefield St, London, WC1N 1PJ, United Kingdom. Phone: +44 20 76794025, fax: + 44 20 7278 4993, e-mail: alees@ion.ucl.ac.uk. The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in Journal of Neurology, Neurosurgery & Psychiatry and any other BMJ PGL products to exploit all subsidiary rights, as set out in our licence (<http://jnnp.bmj.com/fora/licence.pdf>).

AUTHORS: Laura Silveira-Moriyama, MD¹; Petra Schwingenschuh, MD^{2,6}; Angela O'Donnell, RMN³; Susanne A. Schneider, MD²; Pablo Mir, MD, PhD⁴; Fátima Carrillo, MD⁴; Carmen Terranova, MD²; Aviva Petrie, MSc CStat⁵; Donald G. Grosset, MD³; Niall P. Quinn, MD²; Kailash P. Bhatia, MD²; Andrew J. Lees, MD¹.

AFFILIATIONS: ¹Reta Lila Weston Institute of Neurological Studies, UCL Institute of Neurology, London, UK. ²Sobell Department of Motor Neuroscience and Movement Disorders, UCL Institute of Neurology, London, UK. ³Institute of Neurological Sciences, Department of Neurology, Southern General Hospital, Glasgow, UK. ⁴Unidad de Trastornos del Movimiento,

Servicio de Neurología, Instituto de Biomedicina de Sevilla, Hospital
Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, CIBERNED.
Seville, Spain. ⁵Biostatistics Unit, UCL Eastman Dental Institute, London, UK.
⁶Department of Neurology, Medical University Graz, Austria

Keywords: Parkinsonism; tremor; SPECT; smell; SWEDDs

Count Manuscript: 2742 words; abstract: 223 words; 2 tables& 2 figures,
references 37.

ABSTRACT

BACKGROUND: PET and SPECT scanning have 87%-94% sensitivity and 80%-100% specificity to differentiate patients with Parkinson's disease (PD) from control subjects and patients with essential (ET) or atypical tremor. More than 10% of patients diagnosed as early PD can have scans without evidence of dopaminergic deficiency (SWEDDs). We investigated whether smell tests can help identify possible cases with SWEDDs.

METHODS: The 40 item University of Pennsylvania Smell Test (UPSIT) was used to evaluate the sense of smell in 21 SWEDDs patients. We also tested 26 ET patients, 16 patients with a diagnosis of idiopathic adult-onset dystonia (D), 191 non-demented PD patients and 136 control subjects. We used multiple regression analyses to compare the mean UPSIT score in the SWEDDs group with the other 4 groups (ET, D, PD and controls) after adjusting for the effects of relevant covariates.

RESULTS: The mean UPSIT score for the SWEDDs group was greater than in the PD group ($p < 0.001$) and not different from the mean UPSIT in the control ($p = 0.7$), ET ($p = 0.4$), or D ($p = 0.9$) groups. Smell tests indicated a high probability of PD in only 23.8% of SWEDDs as opposed to 85.3% of PD patients.

CONCLUSIONS: In a patient with suspected PD, a high PD probability on smell testing favours the diagnosis of PD, and a low PD probability strengthens the indication for dopamine transporter imaging.

INTRODUCTION

Parkinson's disease (PD) affects as many as 2% of all adults over the age of sixty five[1] and most commonly presents with rest tremor, although the presence of bradykinesia on neurological examination is a sine qua non for its clinical confirmation[2]. The severity of bradykinesia loosely correlates with the extent of the nigrostriatal dopaminergic lesion assessed *in vivo* using dopamine transporter SPECT (DaTSCAN) or F-DOPA PET imaging[3]. DaTSCAN has been licensed in Europe to differentiate PD patients from patients with essential tremor (ET)[4], a condition which is commonly confused with PD in general practice[5]. The diagnostic accuracy of movement disorders specialists in patients with late stage PD can exceed 90%[6]. However, 4 to 14. 7% of early patients enrolled in "de novo" drug trials with a clinical diagnosis of PD have scans without evidence of dopaminergic deficiency (SWEDDs)[7-9], and almost all of these are now thought to be due to clinical misdiagnosis.

Hyposmia occurs in 80-100% of PD cases[10-12] and because smell identification in ET is normal or only mildly decreased, smell tests have also been suggested as a way to help distinguish PD from ET[13,14]. We hypothesized that olfaction would be normal in SWEDDs patients, and that smell tests might be useful in the routine assessment of atypical tremor syndromes where PD is suspected. A more accurate distinction between these commonly confused disorders would also help to reduce the number of non-Parkinsonian patients enrolled in clinical trials. We have administered smell identification tests to 21 patients with SWEDDs and compared the

scores with those of groups of patients with clinically diagnosed PD and normal controls. We have also tested some patients with ET and adult onset dystonia, syndromes which have been considered as possible alternative diagnoses for SWEDDs patients[15,16].

METHODS

Smell testing: The North-American version of the 40 item University of Pennsylvania Smell Identification Test (UPSIT)[17] was used to test odor identification.

Subjects: UPSIT testing was performed in 21 patients who had been diagnosed with PD by a neurologist and who subsequently had normal dopamine transporter SPECT scanning using [123 I]-FP-CIT SPECT (DaTSCAN) (SWEDDS group). Smell tests were also carried out on 26 patients diagnosed with essential tremor by a movement disorder specialist (ET group), and who fulfilled TRIG criteria[18] for definite (n=5), probable (n=17, seven of whom had normal DaTSCAN) or possible ET (n=4, three of whom had normal DaTSCAN); 16 patients with a clinical diagnosis of idiopathic adult onset dystonia (D group), 12 of whom had cervical dystonia, 2 had dystonia with tremor in the arms, one had writer's cramp and one had essential blepharospasm; 191 non-demented patients who fulfilled clinical diagnostic criteria for PD[2] (PD group) and 136 control subjects. All subjects were screened for dementia using the first item of the Part I of the Unified Parkinson's Disease Rating Scale[19] and those who scored ≥ 1 underwent additional Mini Mental State Examination (MMSE)[20]. No patient presented

cognitive complaint or scored less than 27 in the MMSE, except one patient from the SWEDDs group who scored 24/30.

All PD, D and control, and 18 SWEDDs and 16 ET subjects were recruited from patients, visitors and staff at the National Hospital for Neurology and Neurosurgery, in London, UK. Three SWEDDs and 10 ET subjects were recruited from the movement disorder clinic at the Institute of Neurological Sciences, Glasgow, UK. Informed consent was obtained from all subjects according to ethical protocols approved by the regional and local ethics committees.

All the SWEDDs patients had a tremor at rest and difficulty with fine finger movements, and most also had some accompanying limb rigidity. After the normal DaTSCAN result the patients were re-examined and all but two failed to show a clear decrement in speed and amplitude on sequential fine finger movement testing, although most had slowness. A detailed clinical description of 18 of the 21 SWEDDs subjects that were smell tested as part of this study is reported elsewhere[21].

Statistical analysis: To compare the mean UPSIT score in the SWEDDs group with the other 4 groups (ET, D, PD and controls) we used a multiple linear regression analysis for the UPSIT as dependent variable and region of living, gender, age and four group indicator variables as covariates. To compare the mean UPSIT score in the control group with the other 4 groups (SWEDDs, ET, D and PD) we used a multiple linear regression analysis for

the UPSIT as dependent variable and region of living, gender, age, smoking and four group indicator variables as covariates. The assumptions underlying the regression analysis were checked by a study of the residuals and were found to be satisfactory. A significance level of 0.05 was used for all hypothesis testing. We classified the result of the smell test in each patient of the SWEDDs group in terms of high or low probability of PD[22] to see if low PD probability in the smell test could identify potential SWEDDs.

RESULTS

Table 1 shows a summary of clinical data of participants from all groups and Figure 1 illustrates the distribution of UPSIT results in the five patient groups.

Table 1 Summary of data from subjects

Group	N	Age	Smoking habit N (%) smokers	Gender N (%) women	Disease duration	UPSIT score	Subjects with high PD probability[22] on UPSIT
control	136	64.9 (8.8)	13 (11.1%)	64 (47.1%)	-	29.5 (5.3)	18 (13.2%)
ET	26	69.0 (9.3)	5 (22.7%)	18 (69.2%)	11.4 (12.4)	27.9 (4.0)	4 (15.4%)
D	16	66.7 (6.8)	3 (21.4%)	9 (56.3%)	19.7 (9.9)	27.6 (7.5)	4 (25.0%)
SWEDDs	21	65.4 (11.4)	4 (23.5%)	11 (52.4%)	9.3 (9.1)	27.3 (5.0)	5 (23.8%)
PD	191	65.6 (10.7)	12 (6.7%)	77 (40.3%)	10.2 (6.3)	17.6 (6.2)	163 (85.3%)

ET = essential tremor; D = idiopathic dystonia; SWEDDs = patients with scans without evidence of dopaminergic deficit; PD = Parkinson's disease; N = number of subjects; age and disease duration columns display mean (SD) in years. UPSIT = 40 items University of Pennsylvania Smell Identification Test; possible UPSIT result range: 0-40, column displays

mean \pm SD. Smoking habit column displays percentage among those subjects who provided information about tobacco consumption.

The mean UPSIT score for the SWEDDs group was greater than in the PD group ($p < 0.001$, 95% CI for $\beta = -13.7$ to -8.1) and did not differ from the mean UPSIT in the control ($p = 0.7$, 95% CI for $\beta = -2.4$ to $+3.3$), ET ($p = 0.4$, 95% CI for $\beta = -2.2$ to $+5.1$), or D ($p = 0.9$, 95% CI for $\beta = -4.2$ to $+3.6$) groups. Mean UPSIT score in the controls was greater than in the PD group ($p < 0.001$, 95% CI for $\beta = -12.7$ to -10.1) and not different from the mean UPSIT in the ET ($p = 0.5$, 95% CI for $\beta = -2.1$ to $+4.0$), D ($p = 0.6$, 95% CI for $\beta = -3.8$ to $+2.3$), or SWEDDs ($p = 0.7$, 95% CI for $\beta = -3.3$ to $+2.4$) groups. In both regression analyses, age ($p < 0.001$, 95% CI for $\beta = -0.3$ to -0.1), gender ($p = 0.009$, 95% CI for $\beta = -2.7$ to -0.4) and region of living ($p = 0.02$, 95% CI for $\beta = -8.4$ to -0.7) were significant covariates, but smoking was not ($p = 0.06$, 95% CI for $\beta = -3.7$ to $+0.1$).

Table 2 shows clinical data of the 21 SWEDDs patients, including the result of the smell test in terms of score and corresponding PD probability[22] and core signs of parkinsonism.

Table 2 Result and interpretation of smell tests in 21 patients with SWEDDs

Case	Age (y)	Sex	UPSIT score	PD probability[22]	Disease duration (y)	Used dopaminergic drugs?	Parkinsonian signs
1	72	Woman	22	high	5	Yes	S, T, R
2	61	Man	29	low	2	No	T
3	51	Woman	29	low	4	No	T, R

4	75	Woman	32	low	6	No	T, R
5	81	Man	18	high	22	Yes	T
6	78	Woman	27	low	10	Yes	T, S
7	60	Woman	30	low	11	Yes	T, R, S
8	79	Man	33	low	15	No	T
9	69	Man	33	low	7	Yes	T, S
10	38	Man	34	low	3	No	T, S, R
11	68	Man	26	low	20	Yes	T, S, R
12	46	Woman	33	low	5	No	T, S, R
13	50	Woman	29	low	40	Yes	T, S, R
14	66	Man	27	low	5	No	T, S, R
15	71	Woman	23	high	10	No	T, S
16	79	Woman	28	low	7	Yes	T, S, R
17	66	Man	19	high	2	No	T
18	65	woman	33	low	13	No	T, S
19	70	man	18	high	4	Yes	B, T, R
20	65	man	26	low	2	No	B, T, R
21	63	woman	25	low	2	No	S, T, R

SWEDDs = patients initially diagnosed as Parkinson's disease who subsequently had normal DaTSCANS. B = bradykinesia with motor decrement and fatiguing on sequential movement, S = slowness without true bradykinesia, T = tremor, R = rigidity. UPSIT = 40 items University of Pennsylvania Smell Identification Test. Patient 13 had tremor since her early teens. Patient 19 had a Mini Mental State examination score of 24/30.

DISCUSSION

The clinical significance of a normal presynaptic dopaminergic imaging in a patient with a clinical diagnosis of degenerative Parkinsonism is still controversial but follow-up studies suggest that only a minority of SWEDDs patients actually have nigrostriatal denervation or are due to supranigral

causes of parkinsonism (e.g. cerebrovascular disease or cryptic neuroleptic use). A 4-year follow-up study in 150 subjects with suspected presynaptic dopaminergic deficiency who had normal DaTSCANs showed that in only 4 was the diagnosis of degenerative parkinsonism upheld clinically [15]. In a “de novo” therapeutic trial which enrolled 186 patients with a diagnosis of early PD, 21 subjects were found to have normal baseline ^{18}F -dopa PET scans; the scans were repeated after two years in 19 of these patients and all were still normal[9]. In another similar trial[7] 21 of 142 subjects with early “de novo” PD had a normal dopamine transporter scan at baseline and “had no worsening of the ^{123}I -β-CIT uptake at week 40” of follow-up. Furthermore most of these cases did not respond to l-dopa, and another study showed successful withdrawal of antiparkinsonian therapy in 11 patients who fulfilled Queen Square Brain Bank criteria for PD but had normal DaTSCAN [23]. Essential tremor has been considered as a probable diagnosis for a number of these cases[9]. Dopamine transporter imaging with SPECT using [^{123}I]-FP-CIT SPECT (trade name DaTSCAN) is licensed in Europe to differentiate essential tremor (ET) from PD[4] based on data showing a sensitivity between 87% and 94% and specificity of 80% to 100%[24-27]. Our data provide further support for the notion that most cases of SWEDDs do not have Parkinson’s disease as their smell test scores were in the same range as control subjects and significantly different from patients with PD. One of our patients with 2 years of disease duration who fulfilled diagnostic criteria for PD was found to have a normal DaTSCAN and entered the study in the SWEDDs group. The patient scored 14/40 in the UPSIT, indicating high PD probability. During

follow-up his Parkinsonism worsened and a repeat DaTSCAN was abnormal, leading to revised inclusion in the PD group.

Focal or segmental dystonia is a frequent accompaniment in atypical tremor syndromes which masquerade as PD [16]. Smell test scores in the 16 patients with idiopathic adult onset segmental or focal dystonia were in the control range, and did not differ from the scores recorded in the SWEDDs patients. Further larger studies are needed, however, before one can conclude that olfaction is unaffected in dystonia. Most of the patients with ET included in this study did not fulfill the stringent TRIG criteria[18] for definite ET as they presented either with atypical features or short disease duration. However, they had all been seen by movement disorder specialists and carried the label of ET. Their inclusion in this study under the ET label seems reasonable, and is in broad agreement with standard clinical practice, although, in our view some of them might better be labelled as dystonic tremor or atypical tremor. These cases are also the ones most likely to be confused with PD. The ambiguity in current definitions of essential tremor may partly explain the finding of normal smell sense in some series[13,14,28,29] and mild hyposmia in others[30-32]. Even if one accepts that mild smell deficits may be seen in some ET cases, there is still a large gap between the average UPSIT in ET and PD patients.

Although only 29 of the PD patients in the study had undergone a DaTSCAN we believe the number of SWEDDs cases in the entire group is likely to be small as all the patients used fulfilled Queen Square Brain Bank Criteria and

importantly had been under continuous observation in a specialist movement disorder clinic for several years. We have used our data to extrapolate the accuracy of smell tests in the clinical setting of a population with suspected PD based on the assumption that most if not all of them will turn out to have pathologically confirmed PD. It remains conceivable that some of our PD patients might have had SWEDDs but the progressive nature of their illness and the positive response to l-dopa with the emergence of dyskinesias makes it unlikely that the diagnostic error rate would be substantial. As schematized in Figure 2, taking 212 patients with a presumptive diagnosis of PD (all our patients from the PD group plus our patients from the SWEDDs group), the UPSIT gives a high probability of PD in 168 (163/191 -85%- PD and 5/21 - 23%- SWEDDs patients). The smell test result would be accurate in 97%, i.e. of the 168 patients with high PD probability on UPSIT, 163 would be real PD; 95% CI = 94.4% to 99.6%. On the other hand, although the majority of SWEDDs patients (16/21, or 73%) had a low PD probability on the UPSIT, 14% (28 out of 191) of the PD patients also did, indicating that for the 44 subjects with low probability, the smell test would be accurate in 36% (16/44, 95% CI = 23.7% to 51.2%). Given that the overall number of SWEDDs is 21 out of 212 (9.9%, similar to the literature), normal smell testing increases threefold the likelihood that a patient with a clinical diagnosis of PD would have a normal DaTSCAN, and therefore, a diagnosis other than PD.

Five of the 21 SWEDDs patients had a high PD probability on smell testing, indicating that false positive results can occur. Chronic rhinitis[33] and a cold or sinusitis are confounding factors which can lead to temporary or even

permanent smell sense loss[34] and it is possible that the low UPSIT observed in these patients could be due to non-neurological causes. As hyposmia may also be found in persons with mild cognitive impairment and Alzheimer's disease[35], the low MMSE (24/30) in SWEDDs patient number 19 could also be of relevance. If smell tests are to be incorporated into a research protocol, a counsel of perfection would be to arrange an evaluation by an otorhinolaryngologist to exclude other causes of hyposmia, and to apply a stringent cut-off in the MMSE score.

A high UPSIT score suggesting a low probability of PD does not per se make an individual highly unlikely to have PD because there is a significant number of false positives, but it does increase threefold the probability of an alternative diagnosis. In routine clinical practice this finding is relevant and should lead to a careful review of the other clinical findings (for example: Is there a poor response to levodopa? Has there been negligible disease progression? Is there unequivocal bradykinesia?). If doubt increases after review then the findings on smell testing strengthen the clinical indication for a DaTSCAN. Baseline smell testing also offers a less expensive and more convenient alternative to baseline DAT scanning in a clinical research setting where one wants to minimise the possibility of including patients without Parkinson's disease, especially in trials for de-novo patients or early stage PD. The cost of a DaTSCAN is approximately EUR 762 (£672) per patient without the cost of medical personnel[36] while an UPSIT costs US\$ 26.95 (£19)[37], making it at least 30 times cheaper. In addition, there are other smell tests batteries which are even less expensive, such as the 16 item smell

identification test from Sniffin' Sticks, which has been shown to have similar accuracy to the UPSIT in differentiating PD patients from controls[22].

COMPETING INTERESTS: all authors declare no competing interests.

FUNDING This work was funded by the Reta Lila Weston Trust for Medical Research and Dr Silveira-Moriyama is a beneficiary of a Reta Lila Weston fellowship. Dr. Petra Schwingenschuh was funded by the Austrian Science Fund (FWF, Erwin Schrödinger Grant).

REFERENCE LIST

1. de Rijk, MC, Launer, LJ, Berger, K et al. Prevalence of Parkinson's disease in Europe: A collaborative study of population-based cohorts. Neurologic Diseases in the Elderly Research Group. *Neurology* 2000;**54**:S21-S23.
2. Gibb, WR, Lees, AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J.Neurol.Neurosurg.Psychiatry* 1988;**51**:745-752.
3. Scherfler, C, Schwarz, J, Antonini, A et al. Role of DAT-SPECT in the diagnostic work up of parkinsonism. *Mov Disord.* 2007;**22**:1229-1238.
4. National Institute for Health and Clinical Excellence. NICE clinical guideline 35. Parkinson's disease: diagnosis and management in primary and secondary care. Available at URL:

<http://www.nice.org.uk/nicemedia/pdf/cg035niceguideline.pdf>. Update

2006. Accessed Dec. 10, 2008.

5. Quinn, N. Parkinsonism--recognition and differential diagnosis. *BMJ* 1995;**310**:447-452.
6. Hughes, AJ, Daniel, SE, Ben-Shlomo, Y et al. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. *Brain* 2002;**125**:861-870.
7. Fahn, S, Oakes, D, Shoulson, I et al. Levodopa and the progression of Parkinson's disease. *N.Engl.J.Med.* 2004;**351**:2498-2508.
8. Marek, K, Seibyl, J, Parkinson Study Group. Beta-CIT scans without evidence of dopaminergic deficit (SWEDD) in the ELLDOPA-CIT and CALM-CIT studies: long-term imaging assessment. [abstract]. *Neurology* 2008;**60**(S1):A293.
9. Whone, AL, Watts, RL, Stoessl, AJ et al. Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study. *Ann.Neurol.* 2003;**54**:93-101.
10. Doty, RL, Bromley, SM, Stern, MB. Olfactory testing as an aid in the diagnosis of Parkinson's disease: development of optimal discrimination criteria. *Neurodegeneration.* 1995;**4**:93-97.

11. Hawkes, CH, Shephard, BC, Daniel, SE. Olfactory dysfunction in Parkinson's disease. *J.Neurol.Neurosurg.Psychiatry* 1997;**62**:436-446.
12. Muller, A, Mungersdorf, M, Reichmann, H et al. Olfactory function in Parkinsonian syndromes. *J.Clin.Neurosci.* 2002;**9**:521-524.
13. Shah, M, Findley, L, Muhammed, N et al. Olfaction is normal in essential tremor and can be used to distinguish it from parkinson disease. *Clinical Neurophysiology* 2007;**118**:e173.
14. Shah, M, Muhammed, N, Findley, LJ et al. Olfactory tests in the diagnosis of essential tremor. *Parkinsonism.Relat Disord.* 2008;**14**:563-568.
15. Marshall, VL, Patterson, J, Hadley, DM et al. Two-year follow-up in 150 consecutive cases with normal dopamine transporter imaging. *Nucl.Med.Commun.* 2006;**27**:933-937.
16. Schneider, SA, Edwards, MJ, Mir, P et al. Patients with adult-onset dystonic tremor resembling parkinsonian tremor have scans without evidence of dopaminergic deficit (SWEDDs). *Mov Disord.* 2007;**22**:2210-2215.
17. Doty, RL, Shaman, P, Dann, M. Development of the University of Pennsylvania Smell Identification Test: a standardized

microencapsulated test of olfactory function. *Physiol Behav.* 1984;**32**:489-502.

18. Deuschl, G, Bain, P, Brin, M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. *Mov Disord.* 1998;**13**:2-23.
19. Fahn S., Elton R.L., and members of the UPDRS Development Committee. *Recent developments in Parkinson's disease.* Florham Park, NJ: Macmillan Healthcare, 1987:153-163.
20. Folstein, MF, Folstein, SE, McHugh, PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J.Psychiatr.Res.* 1975;**12**:189-198.
21. Schwingenschuh, P, Terranova, C, Carrillo, F et al. Adult onset dystonia can cause tremulous pseudoparkinsonism and is one cause of SWEDDs: Clinical description of 30 cases. *Mov Disord.* 2008;**23**:S164.
22. Silveira-Moriyama, L. and others. The use of a colour coded probability scale to interpret smell tests in suspected Parkinsonism. *Mov Disord.*,2009. In press.
23. Marshall, VL, Patterson, J, Hadley, DM et al. Successful antiparkinsonian medication withdrawal in patients with Parkinsonism and normal FP-CIT SPECT. *Mov Disord.* 2006;**21**:2247-2250.

24. Catafau, AM, Tolosa, E. Impact of dopamine transporter SPECT using 123I-ioflupane on diagnosis and management of patients with clinically uncertain Parkinsonian syndromes. *Mov Disord.* 2004;**19**:1175-1182.
25. Benamer, HT, Oertel, WH, Patterson, J et al. Prospective study of presynaptic dopaminergic imaging in patients with mild parkinsonism and tremor disorders: part 1. Baseline and 3-month observations. *Mov Disord.* 2003;**18**:977-984.
26. Benamer, TS, Patterson, J, Grosset, DG et al. Accurate differentiation of parkinsonism and essential tremor using visual assessment of [123I]-FP-CIT SPECT imaging: the [123I]-FP-CIT study group. *Mov Disord.* 2000;**15**:503-510.
27. Jennings, DL, Seibyl, JP, Oakes, D et al. (123I) beta-CIT and single-photon emission computed tomographic imaging vs clinical evaluation in Parkinsonian syndrome: unmasking an early diagnosis. *Arch.Neurol.* 2004;**61**:1224-1229.
28. Djaldetti, R, Nageris, BI, Lorberboym, M et al. [(123)I]-FP-CIT SPECT and olfaction test in patients with combined postural and rest tremor. *J.Neural Transm.* 2008;**115**:469-472.
29. Busenbark, KL, Huber, SJ, Greer, G et al. Olfactory function in essential tremor. *Neurology* 1992;**42**:1631-1632.

30. Applegate, LM, Louis, ED. Essential tremor: mild olfactory dysfunction in a cerebellar disorder. *Parkinsonism.Relat Disord.* 2005;**11**:399-402.
31. Hawkes, C, Shah, M, Findley, L. Olfactory function in essential tremor: a deficit unrelated to disease duration or severity. *Neurology* 2003;**61**:871-872.
32. Louis, ED, Bromley, SM, Jurewicz, EC et al. Olfactory dysfunction in essential tremor: a deficit unrelated to disease duration or severity. *Neurology* 2002;**59**:1631-1633.
33. Apter, AJ, Gent, JF, Frank, ME. Fluctuating olfactory sensitivity and distorted odor perception in allergic rhinitis. *Arch.Otolaryngol.Head Neck Surg.* 1999;**125**:1005-1010.
34. Murphy, C, Schubert, CR, Cruickshanks, KJ et al. Prevalence of olfactory impairment in older adults. *JAMA* 2002;**288**:2307-2312.
35. Devanand, DP, Michaels-Marston, KS, Liu, X et al. Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. *Am.J.Psychiatry* 2000;**157**:1399-1405.
36. Dodel, RC, Hoffken, H, Moller, JC et al. Dopamine transporter imaging and SPECT in diagnostic work-up of Parkinson's disease: a decision-analytic approach. *Mov Disord.* 2003;**18 Suppl 7**:S52-S62.

37. Sonsonics. Featured Products. Available at URL:

<http://www.senonics.com/shop/pc/home.asp>. Update 2009. Accessed

Feb. 18, 2009.

FIGURE LEGENDS

Legend for Figure 1

Figure 1 UPSIT scores in the five patient groups. The median (the horizontal line) is within the box containing the central 50% of the observations (i.e. the upper and lower limits of the box are the 75th and 25th percentiles): the extremes of the 'whiskers' contain the central 95% of the ordered observations. Outliers are showed as circles. UPSIT = 40 items University of Pennsylvania Smell Identification Test. ET = essential tremor; SWEDDs = patients with scans without evidence of dopaminergic deficit; PD = Parkinson's disease.

Legend to Figure 2

Figure 2 Distribution of PD and SWEDDs patients according to UPSIT. Each circle represents a patient. SWEDDs = patients with a clinical diagnosis of PD and scans without evidence of dopaminergic deficit. PD = Parkinson's disease.



