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Performance on an Alzheimer-Selective Odor Identification Test in Patients with Parkinson's Disease and Its Relationship with Cerebral Dopamine Transporter Activity

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Abstract

Background—Previous studies have shown selective deficits of odor identification in both Parkinson's disease (PD) and Alzheimer's disease (AD). Brief, selective AD smell screening tests have been developed to identify subjects at risk of AD. The disease specificity of such screening tests has not been formally evaluated.

Objective—To evaluate the performance of an Alzheimer-selective odor identification test in patients with PD and its relationship with cerebral dopamine transporter (DAT) activity.

Methods—PD patients (n=44; Hoehn and Yahr stages I–III; 13f/31m; mean age 59.3±10.1) and 44 controls matched for gender and age completed the University of Pennsylvania Smell Identification Test (UPSIT). All patients had PD duration > 1 year and none had evidence of dementia. Using the UPSIT, we calculated performance on the 10 odors previously reported to be selective for AD risk (UPSIT-AD10). A subset of 29 PD patients also underwent brain DAT [¹¹C]β-CFT (2-β-carbomethoxy-3β-(4-fluorophenyl) tropane) PET imaging. DAT binding was assessed in the hippocampus, amygdala, ventral and dorsal striatum.

Results—UPSIT-AD10 scores were significantly lower in the patient (5.8±2.1) compared to the control group (8.6±2.4) (t=5.8, P<0.0001). However, UPSIT-AD10 performance in the PD patients did not correlate with striatal or mesolimbic DAT activity.

Conclusions—Hyposmia in PD and AD overlap and supposed Alzheimer-selective smell screening tests may not be specific for AD. However, the supposed AD-selective hyposmia scores in PD did not correlate with cerebral DAT binding and may reflect a non-dopaminergic olfactory mechanism.

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Keywords

Parkinson's disease; PET; olfaction; dopamine transporter

1. Introduction

Olfactory dysfunction, including impairment in odor identification, is a common non-motor feature of Parkinson's disease (PD) that often precedes the onset of motor manifestations [1]. This is congruent with the PD pathological schema proposed by Braak et. al., with early stages demonstrating alpha-synuclein pathology and neuronal degeneration in the olfactory nucleus and bulb [2]. Odor identification is a task requiring not only intact olfactory function, but also the ability to recognize and name the odor, a learned response, raising the possibility that structures involved in higher order cognitive or memory processing, such as the hippocampus, may be involved. Using the University of Pennsylvania Smell Identification Test (UPSIT) [3], we previously identified 3 odors that were selectively impaired in PD subjects (UPSIT-PD3) [4], and found that this selective hyposmia correlated with striatal, amygdala, and hippocampal dopamine denervation, but most robustly with denervation in the hippocampal area [5]. Thus, hippocampal dopamine denervation in PD may contribute to abnormal cognitive processing of olfactory information leading to selective deficits in odor identification. These neurochemical changes may be caused by either primary neuronal degeneration in brain areas involved in olfactory processing or due to neural fiber disruption from local pathological deposits.

Many studies have shown selective deficits of odor identification in PD. We previously reported that 3 specific odors (banana, licorice and dill pickle) were able to distinguish PD subjects from controls with the greatest accuracy [4]. These 3 odors also had stronger correlations with nigrostriatal dopamine denervation than the total UPSIT. Hawkes and Shephard found that the UPSIT odors pizza and wintergreen were best able to distinguish PD patients from controls [6], while pizza, mint, and licorice were optimal in another British study [7]. Double et al. reported that gasoline, banana, pineapple, smoke, and cinnamon were the odors most affected in Australians with PD using the 12-odor Brief Smell Identification Test (BSIT) [8]. A German study implementing the 12-odor Sniffin' Sticks test reported that licorice, followed by aniseed, pineapple, apple, turpentine, and banana, best separated PD patients from controls [9]. This contrasts with the results of Doty et. al. [10], who reported that olfactory impairment in PD was not confined to a subset of odors. This finding, combined with the fact that several different odors have been reported to be selectively impaired in PD, with few showing up consistently, has led some to believe that there is no convincing evidence for the concept of selective hyposmia in PD [11].

Given that multiple neurotransmitter systems are involved in olfaction [12], it is possible that this concept of olfactory selectivity could be better explained by differential loss of various neurotransmitter systems. Certain odors may be affected primarily by dopamine, while others may be affected by loss of non-dopaminergic neurotransmitters, thus explaining the wide variability in previous studies of hyposmia in PD. Such heterogeneity may also explain why deficits in odor identification have also been reported in Alzheimer's disease (AD), a nondopaminergic neurodegenerative disorder [13]. In AD, olfactory deficits occur early and may be due to the presence of neurofibrillary tangles in the anterior olfactory nucleus [13, 14]. Using the UPSIT, Tabert et al. identified 10 odors (menthol, clove, leather, strawberry, lilac, pineapple, smoke, soap, natural gas, lemon; UPSIT-AD10) that were selectively associated with risk for AD [14]. In this study, we wanted to evaluate the performance of PD patients on the UPSIT-AD10. As we previously found significant correlations between performance on the UPSIT-PD3 and cerebral dopamine transporter (DAT) activity [4,5], we

also wanted to evaluate whether such AD-selective odor identification deficits, if present in PD, had a dopaminergic neural correlate. We hypothesized that patients with PD would perform abnormally on the UPSIT-AD10, but that this abnormal performance would not correlate with dopaminergic denervation.

2. Methods

2.1 Subjects

Forty-four PD patients (Hoehn and Yahr stages I–III; 13f/31m; mean age 59.3 ± 10.1 ; mean duration since symptom onset 3.5 ± 3.5 years) and 44 healthy controls matched for gender and age (59.4 ± 10.8 years) completed the 40-item UPSIT (Sensonics, Inc. Haddonfield, NJ). Performance on the UPSIT-PD3 and UPSIT-AD10 were calculated for each participant. Patients were recruited from the Movement Disorders Clinic at the University of Pittsburgh. Control subjects were recruited from a pool of subjects participating in a normal aging study. All PD patients met UK Parkinson's Disease Society Brain Bank Research Center diagnostic criteria for PD [15] and had a diagnosis of PD for at least 1 year. All participants in this study were nonsmokers and did not have a known history of trauma or concurrent respiratory infection that could interfere with olfactory testing. None of the patients or controls had dementia (defined as Mini-Mental State Examination (MMSE) > 24) [16]. The range of MMSE scores in the patients was 27–30. All participants signed an informed written consent, and the research protocol was approved by the Institutional Review Board of the University of Pittsburgh.

Although DAT positron emission tomography (PET) imaging was offered to all PD patients, only a subset agreed to undergo imaging ($n=29$; 7f/22m). The mean age of these patients was 60.2 ± 10.8 years and the mean duration since symptom onset was 2.7 ± 3.0 years. Overall, patients had mild to moderate disease severity: 10 patients in stage 1, 7 patients in stages 1.5, 5 patients in stage 2, 6 patients in stage 2.5 and one patient in stage 3 of the Hoehn and Yahr classification. The mean motor Unified Parkinson's Disease Rating Scale (UPDRS) score was 15.5 ± 8.2 , with a mean mini-mental status examination (MMSE) score of 29.5 ± 0.8 . Both motor UPDRS testing and PET imaging were performed in the morning after withholding dopaminergic drugs overnight.

2.2 Dopamine transporter PET and MRI imaging

$[^{11}\text{C}]\beta\text{-CFT}$ (2- β -carbomethoxy-3 β -(4-fluorophenyl) tropane) is a specific PET radioligand for the DAT. DAT binding can be assessed by either PET or single photon emission computed tomography (SPECT) radiotracer imaging techniques. PET has the relative advantage of improved spatial resolution allowing assessment of radioligand binding in smaller brain regions. In this study, dynamic $[^{11}\text{C}]\beta\text{-CFT}$ DAT PET imaging with correction for attenuation, scatter and radioactive decay was performed as previously reported [4]. A volumetric spoiled gradient recall MR image (TE=5, TR=25, flip angle=40 degrees, NEX=1, slice thickness=1.5 mm, image matrix=256 $\times$ 192, FOV=24 cm) was collected for each subject using a Signa 1.5 Tesla scanner (GE Medical Systems, Milwaukee, WI). Regions of interest were drawn on the axial MR to include the hippocampus (3–4 slices), amygdala (3–4 slices), and striatum (split into ventral, 4–5 slices, and dorsal portions, 4–5 slices) of each hemisphere and the cerebellum. All MR-drawn slices were summed into volumes of interest (VOIs) for each region and were transferred to the PET data for regional sampling of radioactivity. $[^{11}\text{C}]\beta\text{-CFT}$ binding potential (BP) was calculated using a two-parameter multilinear reference tissue model approach (MRTM2) with the cerebellum as the reference region [17]. Modeling estimates of DAT binding in the hippocampus were set to zero in three subjects and modeling estimates in the amygdala were set to zero in two subjects. This was because the PET modeling approach

yielded slightly negative values due to error variability in the kinetic model in the presence of low tracer binding.

2.3 Statistical Analysis

Group scores on olfactory and cognitive measures were compared using t-tests, except for the comparison of total UPSIT scores between the patient and control group, where a Wilcoxon rank-sum test was used because of non-normal data distribution. Spearman rank correlations were used to evaluate the relationship between the various olfactory measures and cerebral DAT activity. Data were analyzed using SAS (SAS Institute Inc., Cary, NC).

3. Results

3.1 Performance on the UPSIT-AD10 in the PD and control subjects

The mean MMSE scores did not differ between the two groups (PD 29.4 ± 0.8 and controls 29.5 ± 1.0 , ns). Total UPSIT, UPSIT-PD3, and UPSIT-AD10 scores were all significantly lower in the PD subjects compared to the control group (Table 1). There was a significant correlation between performance on the UPSIT-AD10 and UPSIT-PD3 ($R_s = 0.59$, $p = 0.0008$).

3.2 Correlation between UPSIT-AD10 and cerebral DAT binding activity

Table 2 lists the correlation coefficients between the UPSIT-AD10 and regional cerebral [^{11}C] β -CFT binding potential for the 29 PD patients. There was no correlation between UPSIT-AD10 scores and [^{11}C] β -CFT DAT BP in any region, despite our findings that the UPSIT-AD10 score correlates significantly with the UPSIT-PD3 score.

4. Discussion

The present study demonstrates that PD patients have impaired performance on a supposedly AD-selective odor screening test compared to controls. Because hyposmia in AD and PD may overlap, the use of olfactory testing to predict risk of PD or AD in clinical practice needs to be supplemented by other disease-specific markers.

Our finding is not surprising, given that PD patients are able to identify on average only 20 odors correctly on the 40-item UPSIT [4,10]. Although we did not test AD patients in this study, the average score on the UPSIT-AD10 in our PD patients was similar to that reported by Tabert et al. in their AD patients [14], suggesting that the UPSIT-AD10 may not be disease specific. Other studies have shown that PD and AD patients score similarly on the total UPSIT [18]. Although PD and AD may differ in their underlying pathology, both disorders affect olfactory-related brain regions, with studies demonstrating Lewy body and Lewy neurite deposition in the olfactory bulb and anterior olfactory nucleus in patients with PD [2] and the presence of neuritic plaques and neurofibrillary tangles throughout the olfactory pathway in AD [19]. The hyposmia seen in PD and AD may thus be a non-specific feature, potentially resulting from disruption of these olfactory-related neural pathways.

This anatomic pathological explanation of our clinical olfactory findings would argue against the concept of selective hyposmia that has been both reported in AD and PD [6–9,14]. However, we previously found robust correlations between our PD-selective hyposmia score (UPSIT-PD3) and striatal and mesolimbic dopaminergic activity, especially the hippocampus, in the same 29 PD patients [5]. In the present study, we found no significant correlation between the UPSIT-AD10 and *in vivo* nigrostriatal, amygdala, or hippocampal DAT activity in the 29 PD subjects who underwent PET imaging, despite strong correlations between the UPSIT-AD10 and UPSIT-PD3 scores. Olfactory function is a complex task requiring intact olfactory receptors in the olfactory epithelium, proper signal processing at the level of the olfactory bulb

involving glutamate and GABA, and central (higher level) processing involving piriform cortex, hippocampus, amygdala, entorhinal-perirhinal cortex, orbitofrontal, insular and inferior frontal cortex in order to produce a correct identification of the odor name [4,20,21]. Our finding of a lack of correlation between the AD-selective score and dopaminergic denervation could be explained by structural pathology in other parts of the olfactory pathway, but another consideration is that hyposmia in PD involves non-dopaminergic as well as dopaminergic neurochemical substrates. Such a neurochemical hypothesis could provide a potential explanation for the apparent heterogeneity in the selective nature of hyposmia in PD [11].

Multiple neurotransmitters, including acetylcholine, norepinephrine, and serotonin, are involved in olfaction [12]. Dopamine is implicated in the selective hyposmia of PD because of the strong association between nigrostriatal and hippocampal dopamine denervation and performance on the UPSIT-PD3 in PD patients [5], perhaps through abnormal cognitive processing of olfactory information. Dopamine replacement therapy, however, does not improve olfaction in PD [22], suggesting that hyposmia in PD cannot be explained by dopamine deficiency alone.

The role of the cholinergic system in olfaction must be closely examined since cholinergic deficits occur in both AD and PD [23]. Acetylcholine modulates several aspects of central olfactory neuron physiology. Cholinergic projections to the olfactory bulb and piriform cortex arise from the horizontal limb of the diagonal band of Broca [24], which in turn receives feedback from these structures [25]. Cholinergic blockade with scopolamine impairs both olfactory memory and learning [26,27]. Similarly, lesions of the horizontal limb of the diagonal band of Broca impair olfactory memory [25]. It is thus possible that cholinergic deficiency contributes to olfactory dysfunction in PD and explains our PD patients' poor performance on the UPSIT-AD10. Future studies looking at UPSIT-AD10 performance and PET imaging of the cholinergic system in PD patients will be helpful in testing this hypothesis.

Limitations of this study should be kept in mind when interpreting our results. Our sample size was not large and also predominantly male. Women generally outperform men on odor identification testing [28], and further studies with a larger number of female subjects will be necessary to confirm these findings. We used PET imaging to estimate DAT binding in the striatum and lower binding regions such as the amygdala and hippocampus. However, a limitation of this technique is that it does not allow us to reliably quantify cortical DAT activity, making it difficult to correlate olfactory measures with global DAT activity in the brain.

All of our patients had PD for more than 1 year and none had evidence of dementia. These criteria reduce the chances of including patients with concomitant AD neuropathology or patients with dementia with Lewy bodies who may have amyloidopathy [29], but the question of whether PD patients with more deficient UPSIT-AD10 scores are at higher risk of developing dementia needs to be further evaluated.

We conclude that supposed Alzheimer-selective smell screening tests may not be specific for AD and that hyposmia in PD and AD may overlap. However, the supposed AD-selective hyposmia scores in PD did not correlate with cerebral DAT binding and may reflect a non-dopaminergic olfactory mechanism.

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Table 1

Performance on total UPSIT, UPSIT-PD3, and UPSIT-AD10 olfactory measures in patients with PD and matched control subjects.

Olfactory measure	PD (n=44)	Control subjects (n=44)	Statistical significance
Total UPSIT (40)	20.1±9.1	32.5±5.7	$z=4.7$; $P<0.0001$
UPSIT-PD3	1.1±0.9	2.5±0.8	$t=7.7$; $P<0.0001$
UPSIT-AD10	5.8±2.1	8.6±2.4	$t=5.8$; $P<0.0001$

Table 2

²²²Spearman correlation coefficients (with p values) between the UPSIT-AD10 and regional [¹¹C]β-CFT DAT binding potential in the subset of 29 PD subjects who underwent PET imaging.

	UPSIT-AD10
Striatum	0.11 (0.57)
Dorsal striatum	0.083 (0.67)
Ventral striatum	0.15 (0.43)
Amygdala	0.30 (0.12)
Hippocampus	0.24 (0.20)