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SUPRATHRESHOLD ODOR INTENSITY PERCEPTION IN EARLY STAGE PARKINSON'S DISEASE

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Abstract

Background—It is unknown whether Parkinson's disease (PD) influences suprathreshold changes in perceived odor intensity. In Alzheimer's disease, schizophrenia, and the elderly, such perception is reportedly normal. If generally true, this could reflect a core element of the olfactory system insulated to some degree from age- and disease-related pathologies.

Methods—Odor intensity ratings for pentyl acetate were obtained from 29 early stage PD patients when on and off dopamine-related medications (DRMs) and from 29 matched controls.

Results—The ratings were significantly attenuated at the higher odorant concentrations, with the degree of attenuation associated with overall olfactory dysfunction. Ratings were higher in the right than in the left naris of both patients and controls. No associations with DRMs, UPDRS scores, or striatal dopamine transporter activity were found.

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1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

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Conclusions—PD influences suprathreshold estimates of perceived odor intensity, negating the notion that such perception might be spared in this disease. No association with dopaminergic processes was apparent.

Keywords

Parkinson's disease; olfaction; psychophysics; L-DOPA; perception

Introduction

A number of observations suggest that suprathreshold odor intensity ratings may be probing a core element of the olfactory system somewhat independent of other measures.¹ Sparing of suprathreshold intensity function has been reported in older subjects,² Alzheimer's Disease (AD),³ and schizophrenia.⁴ We determined whether the build-up in perceived odor intensity is attenuated in early stage PD patients and, if so, whether the attenuation is associated with overall olfactory function, the use of dopamine-related medications (DRMs), and SPECT imaging of the dopamine transporter.

Methods

Subjects

Fifty eight subjects participated (Table 1), although data from only 56 were available for some analyses. Half were PD patients and half healthy age-, sex- and race-matched controls. All patients met the Gelb et al. criteria for PD⁵ and had lateralized motor deficits for less than 2 years. Informed written consent was obtained and the study protocol was approved by the University's Office of Regulatory Affairs. The normal controls underwent complete neurological examinations and met the exclusion criteria used in screening the PD patients.

Experimental Design

The participants' involvement in the overall research program, of which the testing described in this study was just a part, was spread over the course of two 4-day-long test periods. During one period they were unmediated and during the other DRMs had been taken for a minimum of 6 weeks. Four PD patients completed only the on-DRM 4-day test period because of problems discontinuing their medications, whereas a fifth elected not to take a DRM, having completed only the non-DRM tests. Seventeen were taking carbidopa/levodopa 25/100, 9 the dopamine agonist pramipexole, and 2 the dopamine agonist ropinirole. One control subject did not complete the odor rating test and therefore his data were excluded from the final analyses.

The patients initially tested under the no-DRM condition were *de novo* patients who had never received PD-related medical therapy. Patients who were on carbidopa/levodopa during the first test period were required to stop their medication at least 15 hours prior to the start of the off-DRM test period, whereas those who were taking dopamine agonists were required to stop their medication at least 72 hours before the off-DRM sessions. Reinstitution of medication occurred only after the initial 4-day test period. The order of the

on- and off-DRM test periods was counterbalanced. The controls received all of the same tests, including SPECT imaging. They did not, however, take DRMs.

Olfactory Test Procedure

Odor intensity was assessed using the odor intensity component of the Suprathreshold Odor Rating Test (SORT).⁶ In this test, 100 ml glass sniff bottles containing different concentrations of amyl acetate (10^{-1} , 10^{-2} , 10^{-3} and 10^{-4} vol/vol in USP grade light mineral oil) are presented to the subject. Each stimulus is presented five times in counterbalanced order, resulting in a total of 20 trials. A 15-30 sec interval is interspersed between the stimulus presentations. The subject rated the perceived intensity of the stimuli on an anchored nine-point category scale (1=no smell, 9=extremely strong). The mean of the five presentations for each concentration serves as the subject's score. Scores on the University of Pennsylvania Smell Identification Test (UPSIT)⁷⁻⁹ were used to assess whether the observed disparity between PD and control patients was related to overall olfactory function.

SPECT Imaging Procedures

Dopamine transporter uptake was assessed within the left caudate nucleus, right caudate nucleus, left anterior putamen, right anterior putamen, left posterior putamen and right posterior putamen using Technetium-99m TRODAT.¹⁰⁻¹²

Results

Analyses within the PD cohort

We initially determined, using analysis of variance (ANOVA), whether the intensity ratings were influenced by DRMs, nose side, and the side of hemiparkinsonism. The only significant factors were odorant concentration ($p < 0.0001$) and nose side ($p = 0.021$), reflecting, respectively, a monotonic increase in intensity ratings across increasing odorant concentrations (see Figure 1) and smaller left- than right-side intensity ratings [respective means (SDs) = 3.06 (1.10) & 3.36 (1.19)]. These phenomena were not specific to PD, as is noted in detail in the next section.

No significant correlations were found between L-DOPA equivalents¹³ and either the intensity measures at each concentration level or the slope and intercept functions computed for each subject across the four concentrations (median $r = -0.07$, range -0.22 to 0.05). Lack of meaningful correlations was also noted between the olfactory measures and the UPDRS scores (median $r = 0.06$, range -0.13 to 0.30) and the SPECT DVRs (median $r = -0.03$, range -0.49 to 0.35).

Analyses within the combined PD and control groups

Since the odor ratings were not associated with any of the dopamine-related measures, they were averaged across the no/yes DRM test sessions for the PD patients. For the controls, such averaging was made across the test sessions that had been yoked in sequence to those of the corresponding no/yes DRM sessions. In the few cases where both sessions had not been completed, the single session's value was used in the analysis.

An ANOVA with group (PD, control) as a main factor found lower intensity ratings in the PD patients than in the controls ($p = 0.05$) and, as expected, increases in ratings as concentration increased ($p < 0.0001$). A group by concentration interaction ($p = 0.014$) reflected the more attenuated intensity ratings of the PD patients at the higher odorant concentrations (Figure 1). As in the PD cohort alone, the ratings were lower on the left than on the right side of the nose [$p = 0.01$; respective means (SDs) = 3.45 (0.86) & 3.66 (0.80)]. A similar ANOVA performed on the slope data found the slopes to be flatter in the PD than in the control subjects [$p = 0.04$; respective slope means (SDs) = 1.07 (0.72) & 1.31 (0.52)].

Since most PD patients are not anosmic, the question arises as to whether the build-up in perceived intensity is more reduced in patients with poorer overall smell function. To address this question, we computed a difference value between the intensity ratings of each PD subject (averaged across nose sides and DRM-treatment condition) and that of his or her matched control. This was done separately for each odorant concentration. Pearson correlation coefficients computed between these difference values and UPSIT scores of the PD patients were significant at the two highest stimulus concentrations [respective r (p) values for the 10^{-4} , 10^{-3} , 10^{-2} , and 10^{-1} stimulus concentrations = 0.29 (0.14), 0.24 (0.23), 0.40 (0.037), and 0.54 (0.003)]. This implies that the build-up of perceived intensity was greater in patients with better overall olfactory function.

Discussion

The present study demonstrates that, on average, suprathreshold odor intensity ratings are decreased in PD. This contrasts with reports of lack of such depression in schizophrenia,⁴ AD,³ and older age.² The intensity ratings were unrelated to both DRM therapy and to dopamine transporter activity within the caudate nuclei and putamen. This lack of association with dopamine is in accord with other PD-related studies that find no association of dopamine repletion on tests of odor identification,¹⁴⁻²⁰ detection^{15;20} discrimination,²⁰ and memory,²¹ but contrasts with reports of correlations between UPSIT scores and dopamine transporter binding within the striatum.^{12;22} The basis for the latter disparity is unknown, although it is possible that there is no causal association between changes in the dopamine transporter and olfactory function, *per se*.

Our finding that the magnitude of the PD-related depression in the odor ratings is correlated with UPSIT scores implies that such ratings are not divorced from other olfactory measures even though such ratings are somewhat independent from other types of olfactory measures, as reflected by factor analysis loadings.¹ The correlations among various nominally distinct olfactory tests imply the existence of a "general olfactory acuity" factor akin to the general intelligence factor proposed for tests of intelligence.^{1;23} The degree to which olfactory tests reflect unique physiological properties related to their names is difficult to discern, given differences in individual test reliabilities, odorants, and non-olfactory task demands and operational requirements.⁶

A unique finding of this study is that the intensity ratings were larger for odorants administered to the right than to the left naris in both the PD patients and controls. Previous studies have observed, in normal subjects, a right-side advantage in odor discrimination²⁴

and in intensity judgments to n-butanol,²⁵ but not in odor detection thresholds.^{24;26;27} Reasons for this phenomenon are unknown, although they may reflect lateralized differences in the anatomy and function of the two sides of the brain. In rats, the entire olfactory bulb, including its outer striatum, is larger on the right than on the left,²⁸ and there is a tendency for a similar phenomenon in humans.²⁹ The right anterior hemisphere, which contains a number of structures associated with higher-order olfactory processing, is typically larger than its left counterpart.^{30;31} Functional imaging studies find that odors induce more activity within the right than left piriform and orbitofrontal cortices, core elements of the olfactory system.^{32;33} However, such asymmetries are probably not limited to olfaction. For example, PET studies suggest that the right anterior temporal lobe plays a disproportionate role in higher order gustatory processing,³⁴ and tactile sensitivity in both PD and control subjects is greater on the left side of the body,³⁵ presumably reflecting somatosensory projections to the right hemisphere.

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Figure 1.

Category scale ratings of the intensity of four concentrations of pentyl acetate odors for the PD and control patients. The 9-point rating scale ranged from 1 = no smell to 9 = extremely strong smell. Vertical bars represent standard errors of the mean. See text for details.

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Table 1

Characteristics of study subjects with Parkinson's disease and their matched controls.

	Parkinson's Disease	Matched Normal Controls
Age (mean $\pm$ SD)	63.1 $\pm$ 8.1	62.9 $\pm$ 8.1
Sex (M/F)	16/13	16/13
Mini-Mental State Examine (Mean $\pm$ SD)	29.4 $\pm$ 0.9	29.4 $\pm$ 0.8
Handedness (R/L)	27/2	27/2
Total UPDRS score (Mean $\pm$ SD)	25.9 $\pm$ 10.3	NA
UPDRS Motor Score on DRM (Mean $\pm$ SD)	16.5 $\pm$ 8.0	NA
UPDRS Motor Score off DRM (Mean $\pm$ SD)	20.1 $\pm$ 6.6	NA
Time Since Diagnosis in Months (Mean $\pm$ SD)	16.4 $\pm$ 9.4	NA
Side of Hemi-parkinsonism (Number L, R & B)	17, 12, 0	NA
Hoehn & Yahr Score (Mean $\pm$ SD)	1.4 $\pm$ 0.5	NA
Number of Never, Previous & Current Smokers	15, 14, 0	17, 11, 1