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From sweet to sweat: Hedonic olfactory range is impaired in Parkinson's disease

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ABSTRACT

Introduction: Olfactory dysfunction and neuropsychological symptoms like depression and anhedonia are common non-motor symptoms in Parkinson's disease (PD). The assessment of both functional domains includes clinical examination, olfactory testing, and standardized questionnaires. While olfaction is readily assessed by functional tests, the distinction of anhedonia as a separate symptom from other depressive symptoms is challenging. Thus, a test focusing on the assessment of hedonic olfaction may be helpful in the assessment of neuropsychological symptoms in PD.
Methods: We examined anhedonia by evaluating the perception of pleasantness of odors in PD patients (n = 57) and healthy controls (n = 46). Pleasantness of odors was registered on a visual 9-point scale. For the assessment of anhedonia we used the Snaith-Hamilton-Pleasure-Scale (SHAPS). Depression was evaluated with the Zung Self-Rating Depression Scale and the Beck Depression Inventory II.
Results: PD patients showed a substantial reduction in hedonic olfaction compared to controls (hedonic score: 1.5 vs. 2.2). Hyposmia, one of the most prevalent non-motor symptoms in PD, was a confounding factor. However, even normosmic PD patients showed a reduced hedonic olfaction compared to controls (hedonic score: 1.6 vs. 2.2). Furthermore, we observed a correlation between hedonic olfaction and the SHAPS-score for PD patients even though positive SHAPS-rating was observed in 9% of PD patients only, while no correlation to depression was present.
Conclusion: These findings suggest that reduced hedonic olfaction might be an additional neuropsychological feature, probably giving insights into changes in hedonic tone complementary to hyposmia and depression in PD.

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1. Introduction

Non-motor symptoms in Parkinson's disease (PD) often precede motor symptoms and reduce quality of life (QoL) during disease progression [1]. Today, depression is considered to be one of the most important non-motor symptoms for PD patients because of its high prevalence of up to 40% [2] and its major impact on QoL [1]. Apathy and anhedonia are core symptoms of depression as outlined in the Diagnostic and Statistical Manual of Mental disorders (DSM-V) [3]. Anhedonia, defined as the reduced ability to experience pleasure, particularly affects QoL [4]. The assessment of anhedonia is based on subjectively experienced symptoms reported to the physician (e.g. as in the Snaith-Hamilton-Pleasure-Scale SHAPS) [5]. Anhedonia correlates with reduced ventral striatal activation [6] and may be of hypodopaminergic nature due to degenerating dopaminergic mesolimbic projections in PD. Despite being merely a core symptom of depression, anhedonia and apathy may be specific neuropsychiatric symptoms with different neural substrates, independent of depression in PD [7]. A screening method helping to dissociate these symptoms in PD is an important need for a precise diagnostic workup. Recent work has defined anticipatory anhedonia as anhedonia towards future activities distinct from

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consummatory anhedonia as anhedonia in example to a specific sensory stimulus [8]. Since consummatory anhedonia could be specific for PD [9] we analyzed hedonic olfaction of PD patients using odor sticks as sensory stimuli. A previous study showed that hedonic olfaction in major depression correlates with anhedonia assessed by the Snaith-Hamilton Pleasure Scale (SHAPS) [10]. Reliable olfactory tests like the "Sniffin'Sticks®" (Burghart, Germany) [11] are routinely used to test for hyposmia, one of the most prevalent non-motor symptoms in PD. Neuropathological studies suggest that alpha-synuclein pathology in the olfactory bulb and tract may be closely linked to hyposmia [12]. Olfactory dysfunction is part of a complex cortical network including piriform and orbitofrontal cortex indicating that hyposmia is not solely caused by olfactory bulb degeneration. Loss of dopaminergic innervation to brain regions associated with hyposmia in PD such as the amygdala and the hippocampus may also explain in part impaired odor identification [13].

In this study, we aimed to comprehensively investigate hedonic olfaction in PD. First, we used the "Sniffin'Sticks®" odor identification test to assess hyposmia. To dissociate anhedonia and olfaction we used olfactory sticks with 22 odors assessing intensity and pleasantness of odors. These odors have previously been evaluated in healthy controls for their sensitivity to detect hedonic perception [14]. Furthermore, we performed a comprehensive analysis comparing hyposmia and hedonic olfaction with a self-rated questionnaire for anhedonia using the Snaith-Hamilton-Pleasure-Scale (SHAPS) [5]. Depression was evaluated with the Zung Self-Rating Depression Scale (SDS) and the Beck Depression Inventory II (BDI-II) [15] [16].

2. Material and methods

2.1. Subjects and clinical assessment

PD patients (n = 57; 36 male, 21 female) and controls (n = 46; 22 male, 24 female) were recruited from the movement disorder outpatient center at the University Hospital Erlangen (08/2011-09/2012). Study approval was granted by the ethics committee (No. 4486/2011, FAU Erlangen-Nürnberg, Germany) and all participants gave written informed consent. Patients' demographics and clinical information including age, disease duration, and levodopa equivalent daily dose are summarized in Table 1. PD patients were diagnosed according to the consensus criteria of the German Society of Neurology, in accordance with the UK PDS Brain bank criteria for diagnosis of PD [17]. Motor symptoms were rated according to the Unified Parkinson's Disease Rating Scale (UPDRS) part III [18]. Disease severity was staged using the Hoehn&Yahr scale (H&Y) [19]. Characteristics of the study population (Table 1) revealed no significant age ($p > 0.05$, Student's t-test) and gender ($p = 0.12$, Pearson Chi-Square) differences between PD patients and controls. The mean UPDRS part III was 18.9 (range from 3 to 67) reflected by a mean Hoehn and Yahr (H&Y) stage of 2.1 (range from 1 to 5).

Table 1
Characteristics of study population.

Variable	PD patients (n = 57)	Controls (n = 46)
Sex (male: female)	36:21	22:24
Age (years)	64.1 ± 11.0	60.5 ± 11.7
Female	63.8 ± 11.4	59.6 ± 10.3
Male	64.2 ± 10.9	61.4 ± 13.1
Age at onset (years)	58.8 ± 11.3	
Disease duration (years)	5.8 ± 5.5	
H&Y, mean	2.1 ± 0.9 (0.5–5)	
UPDRS motor- score	19.4 ± 12.9 (0–67)	
LEDD (mg)	396.3 ± 459.4 (0–1700)	
SDS	47.5 ± 11.2 (25–70)**	37.2 ± 7.7 (25–57.5)
BDI-II	9.0 ± 6.4 (0–29)**	4.5 ± 4.5 (0–21)
SHAPS	0.7 ± 1.2 (0–5)	0.4 ± 0.8 (0–4)

**p < 0.01. H&Y = Hoehn & Yahr Scale. UPDRS = Unified Parkinson's Disease Rating Scale. LEDD = Levodopa equivalent daily dose. SDS = Zung Self-Rating Depression Scale. BDI-II = Beck Depression Inventory II. SHAPS = Snaith-Hamilton Pleasure Scale. Data are presented as mean ± SD (range).

2.2. Identification of odors

Odor identification performance was tested using the standardized Sniffin'Sticks® odor identification test [11]. Subjects were required to identify 16 common odors (orange, shoe leather, cinnamon, peppermint, banana, lemon, liquorice, turpentine, garlic, coffee, apple, clove, pineapple, rose, anise, and fish). Odor sticks were presented with four choices for each odor. Odor identification performance was rated as "normosmic" or "hyposmic" using previously established normative data [11].

2.3. Hedonic olfaction

In order to assess the intensity and the hedonic nature of odors a second test with a set of olfactory testing sticks consisting of 22 "hedonic" odors (typically perceived as unpleasant: n-butyric acid ("vomiting smell"), valeric acid ("sweat"), indole ("smell of feces"), garlic, fish, isobutyric acid ("foot perspiration"), skatole ("smell of feces"), turpentine, butter, clove, civette; typically perceived as pleasant: banana, apple, pineapple, peach, vanilla/caramel, peppermint, "Eisbonbon", lemon, coconut, orange, raspberry) was applied as previously described [14]. Note that 10 odors of the Sniffin'Sticks® odor identification test are also featured in this second test. Subjects were asked to rate the intensity of their perception on a scale ranging from 0 to 10 for "very low" to "very high", respectively. The pleasantness of odors was scored using a visual 9-point scale ranging from −4 for "very unpleasant" to +4 for "very pleasant" and 0 for "neutral" (hedonic score: −4 to +4). In addition, the change from a neutral perception is given as absolute hedonic score (absolute hedonic score: 0 to 4) reflecting an absolute measure of perceptual range. The term hedonic range reflects the deviation from neutral of a given odor.

2.4. Questionnaire based examination of anhedonia and depression

Anhedonia was examined using the German version of the SHAPS. Depression was assessed using the SDS [15] and the BDI-II [16]. Both tests have been validated and are routinely used as screening tools for depression in PD [20]. The SHAPS is a self-rated 14-item instrument in which subjects are required to agree or disagree with statements *'I would enjoy … '* covering social interaction, nutrition, and sensory experiences on a 4-point-Likert scale. With the total score ranging from 0 to 14, the SHAPS discriminates between "normal" (total score ≤ 2) and "abnormal" (total score > 2) levels of hedonic tone [5].

2.5. Statistics

Statistical analysis was performed using the SPSS statistic package V.21. Between group analysis was performed by Student's t-test, analysis of covariance (ANCOVA) or analysis of variance (ANOVA) followed by Bonferroni post-hoc testing. Significance level was set at 0.05. Spearman's rho was calculated for correlations at a significance level of 0.05. If not indicated otherwise, all measurements are presented as mean ± standard error of the mean (SEM).

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