Subjective and Objective Olfactory Abnormalities in Crohn’s disease

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Abstract

The pathogenesis of Crohn’s disease (CD) is still unknown, but the involvement of the olfactory system in CD appears possible. No study to date has systematically assessed the olfactory function in CD patients. We investigated the olfactory function in CD patients in active (n = 31) and inactive disease (n = 27) and in a control group of age- and sex-matched healthy subjects (n = 35). Subjective olfactory testing was applied using the Sniffin’ Sticks test. For olfactory testing, olfactory event–related potentials (OERPs) were obtained with a 4-channel olfactometer using phenyl ethyl alcohol (PEA) and hydrogen sulfide (H2S). Carbon dioxide (CO2) was employed as control stimulus, and chemosomatosensory event–related potentials (CSSERPs) were registered. Results of the Sniffin’ Sticks test revealed significantly different olfactory hedonic judgment with increased olfactory hedonic estimates for pleasant odorants in CD patients in active disease compared with healthy subjects. A statistically significant trend was found toward lower olfactory thresholds in CD patients. In objective olfactory testing, CD patients showed lower amplitudes of OERPs and CSSERPs. Additionally, OERPs showed significantly shorter N1- and P2 latencies following stimulation of the right nostril with H2S in CD patients in inactive disease compared with controls. Our study demonstrates specific abnormalities of olfactory perception in CD patients.

Key words: Crohn’s disease, olfaction, olfactory event–related potentials

Introduction

The pathogenesis of Crohn’s disease (CD) is still unknown. Immunoregulatory, genetic, and environmental aspects seem to represent the interactive cofactors of the disease (Shanahan 2001). Due to the rising incidence of CD in countries with advanced systems of conservation and refinement in the food processing industry, an impact of nutritional factors in the development and perpetuation of CD has been discussed since the 70s (Brahme et al. 1975). In particular, several studies showed an increased consumption of refined sugar in patients with CD (Martini and Brandes 1976; Miller et al. 1976; Heaton et al. 1979; Thornton et al. 1979; Mayberry et al. 1981; Tragnone et al. 1995), and an association was found between preillness diet and subsequent development of CD (Reif et al. 1997). More detailed pathological mechanisms explaining the relation between nutritional factors and the development of CD are still lacking. It is uncertain whether changes in olfactory function might explain changes in nutritional habits in CD patients. According to current literature, no study to date has systematically assessed the olfactory function in CD patients. Involvement of the olfactory system in CD appears possible for different reasons. On the one hand, analogous to the cancer-related anorexia/cachexia syndrome (Mantovani et al. 2001), the increased tumor necrosis factor (TNF)-α levels described in the blood and intestinal mucosa of CD patients (Autschbach et al. 1995; Komatsu et al. 2001) might lead to changes in appetite, taste, and olfactory function. Research in animal models suggests that TNF-α directly causes dysfunction of olfactory neurons (Turner et al. 2010; Sultan et al. 2011). Furthermore, a zinc deficiency is described in CD patients (Griffin et al. 2004; Filippi et al. 2006), and several studies showed that a zinc deficiency can lead to olfactory dysfunction (Couinaud 1984; Tomita 1996). On the other hand,
There is evidence of increased olfactory sensitivity and olfactory pleasure in higher hunger state (Albrecht et al. 2009; Stafford and Welbeck 2011; Trellakis et al. 2011).

A better understanding of the olfactory function in CD patients may contribute to better acceptance of nutritional therapy, which is an established therapeutic option in quiescent and acute CD (Schwab et al. 1998; Verma, Kirkwood et al. 2000; Verma, Holdsworth et al. 2001). In acute CD, remission rates of nutritional therapy (elemental diet, oligopeptide diet) are comparable with those of corticosteroids, but the tolerance of nutritional therapy is poor (Schwab et al. 1998). Taste and smell aversions in CD patients have been hypothesized as a reason for poor acceptance (Lindor et al. 1992; Gorard et al. 1993; Schwab et al. 1998).

In order to investigate the olfactory function in CD patients, we assessed olfactory functioning in patients with active and inactive CD by subjective and objective means in the present study.

Materials and methods

Subjects

A total of 58 patients with CD participated in the study. Patients with active CD were recruited at the Department of Medicine I in the University Hospital Erlangen, where they were admitted because of exacerbation of the disease. Patients with quiescent disease were recruited by a campaign supported by the DCCV, the German patients’ organization for inflammatory bowel disease (IBD). Patients were categorized according to Crohn’s Disease Activity Index (CDAI) into 2 groups, patients with inactive CD (CDAI < 150) and patients with active CD (CDAI ≥ 150). The CD group contained 27 patients with active disease (CDAI ≥ 150) and 31 patients with quiescent disease (CDAI < 150). A control sample of 35 age- and sex-matched healthy volunteers were included in the study (Table 1). There were no significant differences between the 3 groups (healthy controls, patients with inactive CD, and patients with active CD) concerning smoking and alcohol consumption. There was a difference between the 3 groups in body mass index (BMI) (P < 0.05) with a lower BMI in patients with active CD compared with healthy subjects (P < 0.05) (Table 1). CD progress and CD status according to the Vienna classification were not significantly different between the CD groups (patients with inactive CD and patients with active CD).

Laboratory parameters

Blood samples were obtained and analyzed for nutritional status (protein, albumin, folate acid, vitamin B12, vitamin

Table 1  Patient characteristics in reference to age, gender, and BMI

<table>
<thead>
<tr>
<th></th>
<th>Healthy subjects (n = 35)</th>
<th>Patients with inactive CD (n = 31)</th>
<th>Patients with active CD (n = 27)</th>
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<tr>
<td>Age (y) (mean ± SD)</td>
<td>37.6 ± 13.3</td>
<td>39.7 ± 13.0</td>
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<tr>
<td>Gender (female/male) (n)</td>
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<td>14/13</td>
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<td>BMI (kg/m²) (mean ± SD)</td>
<td>25.5 ± 3.8</td>
<td>24.5 ± 4.0</td>
<td>23.1 ± 3.2</td>
<td>P &lt; 0.05</td>
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ns, not significant; SD, standard deviation.
A, and zinc), TSH, and inflammation. We determined CRP using the SYNCHRON CX Test (Beckman Coulter Ireland Inc.). The principle of this quantitative turbidimetric test is that latex particles coated with specific anti-human CRP are agglutinated when mixed with samples containing CRP. The agglutination causes an absorbance change, dependent upon the CRP content of the patient sample that can be quantified by comparison from a calibrator of known CRP concentration.

Nutritional habits

A scanner-readable objective food frequency questionnaire (FFQ) was used to assess the subjects/patient’s usual food intake. Details were described earlier (Zopf et al. 2009).

Subjective olfactory testing

Prior to testing, the participants’ medical history was assessed in order to control for disturbances of the olfactory system. All subjects suffering from known anosmia or hyposmia were excluded. The standard odor of the Sniffin’ Sticks test were employed for olfactory testing (Hummel et al. 1997). All participants clearly perceived the odorants, that is, all stimuli were presented at suprathreshold concentrations. The interval between stimulus presentations was set at 30 s.

Participants performed the 3 subtests of the original Sniffin’ Sticks test: Threshold, odor discrimination, and identification. The standard testing procedure was extended by visual analogue rating scales for the assessment of odor intensity and hedonics, as described earlier (Markovic et al. 2007). As test stimuli for subjective odor ratings, the 16 smells of the Sniffin’ Sticks identification test were used (Hummel et al. 1997; Kobal et al. 2000). The relative scaling for “unpleasantness/pleasantness” ranged from −10 to +10 visual analogue rating units (VARU) and for “very low intensity/very high intensity” from 0 to +20 VARUs, represented by a physical length of 20 cm on paper. Subjects marked the perceived intensity and hedonic valence with a pencil on the scales presented.

For statistical analyses, we calculated averages of intensity and pleasantness ratings across all odorants. Averages of relative hedonic ratings and additionally, as a measure of rating range, averages of absolute hedonic estimates were calculated, that is, the absolute values of positive and negative ratings were averaged. Additionally, the hedonic ratings were considered separately for unpleasant (turpentine, garlic, and fish), neutral (shoe leather, liquorice, coffee, and clove), and pleasant odorants (orange, cinnamon, peppermint, banana, lemon, apple, pineapple, rose, and anise). These classifications were based on the results of the database Hedos-F (hedonic ratings: negative odorants: −10 to −1; neutral odorants: −1 to +1; positive odorants: +1 to +10) (Markovic et al. 2007; Thuerauf et al. 2008).

Objective olfactory testing

Objective olfactory testing was applied using a 4-channel olfactometer OM 2 s (Burghart).

Olfactory event-related potentials (OERPs) were obtained separately for each nostril using phenyl ethyl alcohol (PEA, 100 ppb) as a pleasant rose-like odorant and hydrogen sulfide (H₂S, 2–6 ppm) as a putrid, rancid odorant. Both odorants exclusively stimulate the olfactory system (Doty et al. 1978; Hummel et al. 1991). Chemosomatosenory event-related potentials (CSSERPs) were obtained using carbon dioxide (CO₂) as control stimulus, specifically stimulating the trigeminal system.

PEA-, H₂S-, and CO₂-stimu (stimulus duration: 250 ms) were presented in blocks employing series of 15 stimuli of each stimulus type (measuring sequence: PEA right nostril, PEA left nostril, H₂S right nostril, H₂S left nostril, CO₂ left nostril, CO₂ right nostril; interstimulus interval: 45 ms; duration of the complete recording session: 68 min). Each stimulus odor was presented a Teflon tube of 4 cm with an inner diameter of 5.5 mm. The flow rate was held constant at 140 mL/s, as were room temperature (37°C) and humidity (80%).

Event-related potentials were recorded in the EEG (bandpass, 0.1–30 Hz) using fixed electrodes at the positions C3, C4, FZ, CZ, and PZ of the 10/20 system referenced to an electrode at the inion. Eye blinks were monitored by means of an additional EEG electrode referenced to the anion.

After analog to digital conversion (AD-converter MIO, 16 bit, National Instruments; sampling rate: 250 Hz), records of 2048 ms were obtained and transferred to offline data analysis (EPEvaluate 4.2.3/Labview) on a desktop PC. Records that might have been affected by movements or eye blinks were excluded from further analysis. The remaining records were averaged separately for the 6 categories (PEA right nostril, PEA left nostril, H₂S right nostril, H₂S left nostril, CO₂ left nostril, and CO₂ right nostril). Subsequently, 3 base-to-peak amplitudes (P1, N1, and P2) and 2 peak-to-peak amplitudes (P1/N1 and N1/P2) were evaluated. The latencies of the 3 base-to-peak amplitudes (L-P1, L-N1, and L-P2) were measured relative to stimulus onset.

During the entire measuring session, subjects were comfortably seated in an air-conditioned chamber. Headphones were used for acoustical stimulation with white noise (50 dB), which was applied continuously in order to mask switching clicks of the stimulator. In order to stabilize vigilance (and/or motor coordination), subjects were requested to perform

<table>
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<th>Table 2</th>
<th>Medical treatment in CD patients in active and inactive status</th>
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<td>Patients with inactive CD</td>
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<tr>
<td>Corticosteroids</td>
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<td>Salicylates</td>
<td>14</td>
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<tr>
<td>Immunosuppressives</td>
<td>8</td>
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<tr>
<td>No medications</td>
<td>10</td>
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a simple task on a video screen: They had to keep a small square, which could be controlled by a joystick, inside a larger one, which moved around unpredictably.

Statistics

SPSS/Version 15.0 for Windows (SPSS Inc.) was used for all calculations. Descriptive statistical methods were analyzed. The data did not deviate from the normal distribution according to the Kolmogorov–Smirnov Test. Therefore, data of the Sniffin’ Stick Test and data of evoked potentials were tested with parametric tests. Differences between the 3 diagnosis groups (healthy controls, patients with inactive CD, and patients with active CD) were tested for statistical significance by applying univariate variance analyses (ANOVA). Post hoc tests for differences between 2 groups were calculated with t-tests with an adjustment for multiple testing (Bonferroni corrected significance level). Chi-square test was used for categorical variables. All statistical tests were 2 sided. The significance level before multiple testing was set at $\alpha = 0.05$.

Results

Subjective olfactory testing

Threshold, discrimination, and identification

A statistical trend was found toward a different olfactory threshold between the 3 groups, with a lower olfactory threshold in patients with inactive CD compared with healthy controls (mean ± SEM: healthy: $6.2\pm0.41$; patients with inactive CD: $7.0\pm0.45$; ANOVA: $df = 2, F = 2.7, P = 0.073, P < 0.1$; the threshold test is based on dilution steps, i.e., higher numerical values indicate higher dilution steps = lower thresholds).

No differences between the groups were seen in discrimination (mean ± SEM: healthy: $11.8\pm0.34$; patients with inactive CD: $11.6\pm0.34$; patients with active CD: $10.93\pm0.95$; ANOVA: $df = 2, F = 1.35, P = 0.27$) and identification (mean ± SEM: healthy: $13.53\pm0.23$; patients with inactive CD: $12.83\pm0.29$; patients with active CD: $12.8\pm0.36$; ANOVA: $df = 2, F = 2.17, P = 0.12$).

Intensity ratings

The analysis of intensity ratings revealed no difference between the groups (mean ± SEM: healthy: $12.5\pm0.39$; patients with inactive CD: $12.75\pm0.59$; patients with active CD: $12.85\pm0.54$; ANOVA: $df = 2, F = 0.13, P = 0.87$).

Hedonic estimates

A statistical trend was observed for relative hedonic ratings (mean ± SEM: healthy: $1.13\pm0.28$; patients with inactive CD: $1.68\pm0.31$; patients with active CD: $2.21\pm0.42$; ANOVA: $df = 2, F = 2.7, P = 0.075, P < 0.1$) and absolute hedonic ratings (mean ± SEM: healthy: $3.71\pm0.17$; patients with inactive CD: $4.30\pm0.17$; patients with active CD: $4.48\pm0.43$; ANOVA: $df = 2, F = 2.4, P = 0.095, P < 0.1$, with the highest hedonic rating in the patients with active CD. Considered separately for pleasant odorants, ANOVA revealed a significant difference between the groups with a significantly higher hedonic rating for positive odorants in patients with active CD compared with healthy controls (mean ± SEM: healthy: $2.99\pm0.31$; patients with inactive CD: $3.95\pm0.33$; patients with active CD: $4.26\pm0.49$; ANOVA: $df = 2, F = 3.5, P = 0.035, P < 0.05$; Post hoc pairwise comparisons: Healthy controls – patients with inactive CD: Mean difference: $-0.96, SEM = 0.50, P = 0.177$; Healthy controls – patients with active CD: mean difference: $-1.27, SEM = 0.51, P = 0.045, P < 0.05$; patients with inactive CD – patients with active CD: mean difference: $-0.31, SEM = 0.53, P = 1.0$) (Figure 1). ANOVA revealed no significant difference between the groups for neutral odorants (mean ± SEM: healthy: $0.11\pm0.44$; patients with inactive CD: $0.4\pm0.44$; patients with active CD: $0.85\pm0.54$; ANOVA: $df = 2, F = 0.61, P = 0.54$) and negative odorants (mean ± SEM: healthy: $-3.14\pm0.46$; patients with inactive CD: $-3.49\pm0.54$; patients with active CD: $-2.12\pm0.73$; ANOVA: $df = 2, F = 1.45, P = 0.24$).

Olfactory event-related potentials

The highest amplitudes of OERPs were seen at CZ and PZ.

Amplitudes

ANOVA revealed significantly different base-to-peak N1 amplitudes between the groups.

Figure 1 Means and SEMs of subjects’ summed hedonic estimates for positive odorants. White column: healthy controls; hatched column: patients with inactive CD; black column: patients with active CD, asterisks indicate a statistically significant difference, *$P < 0.05$. 
Following stimulation of the right nostril with PEA, N1 amplitudes were significantly lower in patients with active CD and tended to be lower in patients with inactive CD compared with healthy controls at CZ (mean ± SEM: healthy: −6.3 ± 1.0; patients with inactive CD: −3.7 ± 0.7; patients with active CD: −2.6 ± 0.8; ANOVA: df = 2, F = 5.04, P = 0.009, P < 0.05; Post hoc pairwise comparisons: healthy controls − patients with inactive CD: mean difference: −2.6, SEM = 1.0, P = 0.075; Healthy controls − patients with active CD: mean difference: −3.6, SEM = 1.0, P = 0.01, P < 0.05; patients with inactive CD − patients with active CD: mean difference: −1.1, SEM = 1.2, P = 1.0) (Figure 2) and at PZ (mean ± SEM: healthy: −5.9 ± 0.9; patients with inactive CD: −3.5 ± 0.6; patients with active CD: −2.7 ± 0.7; ANOVA: df = 2, F = 4.93, P = 0.01, P < 0.05; Post hoc pairwise comparisons: Healthy controls − patients with inactive CD − patients with active CD: mean difference: 0.5, SEM = 1.0, P = 0.065; patients with inactive CD − patients with active CD: mean difference: 2.1, SEM = 1.0, P = 0.099, P < 0.05; Post hoc pairwise comparisons: Healthy controls − patients with active CD: mean difference: −3.2, SEM = 1.0, P = 0.034, P < 0.05; patients with active CD − patients with inactive CD: mean difference: 1.3, SEM = 1.0, P = 0.046, P < 0.05; patients with inactive CD − patients with active CD: mean difference: 3.8, SEM = 1.0, P = 0.012, P < 0.05; ANOVA: df = 2, F = 4.06, P = 0.021, *P < 0.05; *P < 0.1.

Additionally, ANOVA revealed significantly different peak-to-peak P1–N1 amplitudes between the groups. Significantly lower P1–N1 amplitudes in patients with active CD compared with healthy controls were seen at PZ following stimulation of the left nostril with PEA (mean ± SEM: healthy: 7.3 ± 0.6; patients with inactive CD: 6.2 ± 0.7; patients with active CD: 4.9 ± 0.7; ANOVA: df = 2, F = 3.07, P = 0.05; Post hoc pairwise comparisons: Healthy controls − patients with inactive CD − patients with active CD: mean difference: 1.1, SEM = 0.9, P = 0.67; Healthy controls − patients with active CD: mean difference: 2.5, SEM = 1.0, P = 0.046, P < 0.05; patients with inactive CD − patients with active CD: mean difference: 1.3, SEM = 1.0, P = 0.55) (Figure 3). ANOVA revealed significantly different peak-to-peak P1–N1 amplitudes between the groups following stimulation of the right nostril with PEA at CZ, with a trend to lower amplitudes in patients with inactive CD compared with healthy controls (mean ± SEM: healthy: 8.2 ± 0.6; patients with inactive CD: 6.1 ± 0.7; patients with active CD: 6.1 ± 0.7; ANOVA: df = 2, F = 3.2, P = 0.046, P < 0.05; Post hoc pairwise comparisons: Healthy controls − patients with inactive CD: mean difference: 2.0, SEM = 0.9, P = 0.09; Healthy controls − patients with active CD: mean difference: 2.1, SEM = 1.0, P = 0.12; patients with inactive CD − patients with active CD: mean difference: 0.1, SEM = 1.0, P = 1.0) (Figure 3). Following stimulation of the left nostril with H2S, a trend to lower P1–N1 amplitudes in CD patients was observed at CZ (mean ± SEM: healthy: 8.5 ± 0.7; patients with inactive CD: 6.4 ± 0.8; patients with active CD: 6.6 ± 0.8; ANOVA: df = 2, F = 2.38, P = 0.099, *P < 0.05, *P < 0.1.

**Figure 2** Means and SEMs of the base-to-peak amplitude N1 of the OERPs (PEA right, H2S left). White column: healthy controls; hatched column: patients with inactive CD; black column: patients with active CD; asterisks indicate a statistically significant difference, *P < 0.05, *P < 0.1.
P < 0.1) (right nostril with H2S at PZ: mean ± SEM: healthy: 6.9 ± 0.6; patients with inactive CD: 6.3 ± 0.7; patients with active CD: 5.1 ± 0.7; ANOVA: df = 2, F = 1.5, P = 0.23).

No significant difference between the 3 groups occurred for the base-to-peak-amplitudes P1 and P2 and for the peak-to-peak-amplitude N1/P2.

Latencies

Following stimulation of the right nostril with H2S, significantly shorter N1 latencies (CZ: mean ± SEM: healthy: 379 ± 21.3; patients with inactive CD: 311 ± 18.8; patients with active CD: 337 ± 17.9; ANOVA: df = 2, F = 3.29, P = 0.04, P < 0.05; Post hoc pairwise comparisons: Healthy controls − patients with inactive CD: mean difference: 68.1, SEM = 26.8, P = 0.039, P < 0.05; Healthy controls − patients with active CD: mean difference: 42.4, SEM = 29.0, P = 0.44; patients with inactive CD − patients with active CD: mean difference: −25.7, SEM = 29.0, P = 1.0) and P2 latencies were recorded in patients with inactive CD compared with healthy controls (CZ: mean ± SEM: healthy: 607 ± 25.8; patients with inactive CD: 512 ± 20.2; patients with active CD: 549 ± 30.0; ANOVA: df = 2, F = 3.99, P = 0.022, P < 0.05; Post hoc pairwise comparisons: Healthy controls − patients with inactive CD: mean difference: 94.8, SEM = 33.8, P = 0.019, P < 0.05; Healthy controls − patients with active CD: mean difference: 58.1, SEM = 36.6, P = 0.35; patients with inactive CD − patients with active CD: mean difference: −36.7, SEM = 36.6, P = 0.96) (Figure 4).

Additionally, a trend toward different N1–P2 amplitudes

Chemosomatosensory evoked potentials

Following stimulation with CO2, the highest chemosomatosensory-evoked potentials (CSSEP) amplitudes occurred at CZ and PZ.

The ANOVA revealed significantly different N1–P2 amplitudes following stimulation of the right nostril with CO2, with significantly lower amplitudes in patients with inactive CD compared with healthy controls at CZ (mean ± SEM: healthy: 26.5 ± 2.7; patients with inactive CD: 20.9 ± 2.2; patients with active CD: 17.0 ± 2.4; ANOVA: df = 2, F = 3.67, P = 0.03, P < 0.05; Post hoc pairwise comparisons: Healthy controls − patients with inactive CD: mean difference: 5.6, SEM = 3.0, P = 0.28; Healthy controls − patients with active CD: mean difference: 9.5, SEM = 4.0, P = 0.029, P < 0.05; patients with inactive CD − patients with active CD: mean difference: 3.9, SEM = 4.0, P = 0.84) (Figure 5).
was observed at PZ following stimulation of the right nostril with CO₂ (mean ± SEM: healthy: 24.9 ± 2.2; patients with inactive CD: 17.4 ± 2.0; ANOVA: df = 2, F = 2.39, P = 0.098, P < 0.1) and following stimulation of the left nostril with CO₂ (mean ± SEM: healthy: 19.2 ± 1.4; patients with inactive CD: 15.1 ± 1.4; patients with active CD: 14.7 ± 1.9; ANOVA: df = 2, F = 2.69, P = 0.074, P < 0.1) with lower amplitudes in CD patients.

A trend toward different P1–N1 amplitudes with lower amplitudes in CD patients was observed at PZ following stimulation of the right nostril with CO₂ (mean ± SEM: healthy: 10.1 ± 1.1; patients with inactive CD: 7.5 ± 1.2; patients with active CD: 6.5 ± 1.2; ANOVA: df = 2, F = 2.99, P = 0.056, P < 0.1) and following stimulation of the left nostril with CO₂ (mean ± SEM: healthy: 8.8 ± 0.8; patients with inactive CD: 6.2 ± 0.9; patients with active CD: 6.5 ± 1.0; ANOVA: df = 2, F = 2.72, P = 0.072, P < 0.1).

The CSSEP latencies did not differ between the groups.

**Discussion**

Our results demonstrate specific abnormalities of olfactory perception in CD patients.

The increase in olfactory pleasure and the trend to higher olfactory sensitivity in CD patients could be interpreted as a natural counter regulation against malnutrition. Food intake is regulated by homeostatic and hedonic sensory factors (Saper et al. 2002; Rolls 2011). There is some evidence that olfactory sensitivity changes with the actual state of satiety. Albrecht et al. (2009) showed an increase of olfactory sensitivity and a decrease of pleasantness ratings from hunger to satiety state. Stafford and Welbeck (2011) found that high hunger state increases olfactory sensitivity to neutral but not food odors. Berg et al. (1963) demonstrated higher olfactory sensitivities after a satiating meal. Other investigators found no relationship between olfaction and satiety state (Janowitz and Grossman 1949; Zilstoff-Pedersen 1955; Turner and Patterson 1966; Crumpton et al. 1967; Koelega 1994).

The increased olfactory pleasure in CD patients found in our study might be explained as due to reduced absorption of nutrients as the patients suffered from diarrhea and had lower BMIs than controls. This theory is also supported by the fact that highest hedonic ratings were seen in the patients with active disease (CDAI ≥ 150). It should be discussed if the observed effects for a difference in hedonic ratings are based upon the fact that more pleasant compared with neutral and unpleasant odors are included in the Sniffin’ Sticks identification test, so that statistical power is higher for pleasant compared with neutral and unpleasant odors. A study from our laboratory of a large human population of 201 participants (data sets) revealed that the overall hedonic estimate for...
the sum of all odors was 12.0 ± 17.0 VARU (unpleasantness/pleasantness scale: range = −100 to +100), indicating that the test is relatively balanced for pleasant and unpleasant odors with a slight tendency toward pleasant odors (Markovic et al. 2007). The results of the ANOVAs for neutral and for unpleasant odorants found neither significant differences nor statistical tendencies. Thus, it is unlikely that the difference in hedonic ratings is mainly due to different statistical power.

We found significant differences in BMI values between the groups investigated with higher BMI values in healthy controls. Concerning the relationship between obesity, BMI, and olfactory hedonics, some fMRI studies have shown greater activation in specific brain regions to viewing high-calorie foods, or anticipation of food delivery, in people with obesity, higher BMI, or binge eating disorder (Ziauddeen et al. 2012; Brooks et al. 2013). These results point to higher hedonics in subjects with higher BMI, but in our study, we found higher hedonic rating for positive odorants in patients with active CD presenting lower BMIs than healthy controls. Another study in obesity found no relation between BMI and hedonic response (Thompson et al. 1977). Based on these inconsistent results, it is more likely that the higher hedonic rating for positive odorants in patients with active CD represents a specific finding and not a secondary effect of BMI differences between the groups.

In objective olfactory testing, CD patients showed lower amplitudes of OERPs compared with healthy subjects. Furthermore, shorter N1- and P2 latencies in OERPs were seen in CD patients following stimulation of the right nostril with H2S. Reduced amplitudes in CD patients appeared not only in OERPs, but also in CSSEPs and do not seem to be specific for olfaction. Reduced amplitudes might be caused by nonspecific effects, like sedation. It has been described that N1–P2 amplitudes are higher under attend than ignored conditions (Geisler and Murphy 2000). It might be possible that healthy participants allocated more attention to olfactory and chemosensory stimuli than patients. Furthermore, a generalized neuronal hypoexcitability in CD cannot be ruled out. Animal studies revealed that inflammation via cytokines, including TNFα, has profound effects on the innervation of affected tissues, including altered neuronal excitability and neurotransmitter release (Motagally, Lukewich et al. 2009; Motagally, Neshat et al. 2009). According to current literature, cortical excitability in IBD has not been systematically investigated.

One hypothesis for the shorter latencies following stimulation of the right nostril with H2S in CD patients could be a faster identification of H2S. P2 amplitudes seem to reflect a sensory integration mechanism, and P2 latencies seem to correlate with odor identification (Evans et al. 1995). Exposure to an odorant induces greater sensitivity to future exposure to the same odorant (Rabin and Cain 1986). H2S is an unpleasant, putrid odorant. Putrid infections occur in CD. Therefore, CD patients might be more sensitive to H2S because of higher preexposure.

A limitation of our study is that olfactory thresholds were determined only for 1 odorant, that is, n-butanol. Another limitation of the study is that event-related potentials were recorded only following chemical stimulation (OERPs and CSSEPs). Because we detected relatively unspecific effects over all latencies and amplitudes in CD patients, additional acoustical stimulation would have been helpful in order to control for an altered central processing of sensory information in the patient group. Thus, linking the results of the subjective and the objective sensory data is limited. Nevertheless, it should be mentioned that a negative correlation between pleasantness and amplitudes of the late positive OERP component (OERP) often termed P2 or P3 could be demonstrated for the individual perception of an odorant (Lundström et al. 2006) (equivalent nomenclature P3 = P2: Hummel T, personal communication).

Regarding the medication used in our patient group, Steinbach et al. (2013) found minimal and nonsignificant effects of treatment with low-dose oral cortisone, azathioprine, or 5-ASA on olfactory and gustatory functions. However, high doses of oral cortisone are known to be helpful in patients suffering from olfactory dysfunctions (Steinbach et al. 2008). Reversible dysgeusia has been reported following treatment with azathioprine (Ellul et al. 2007).

Interestingly, shortened latencies following stimulation with H2S occurred only on the right side. A relative favoring of the right cerebral hemisphere for some olfactory tasks has been suggested. Lateralization of the human olfactory cortex at the level of secondary olfactory cortex with unilateral activation of the right orbitofrontal cortex, as a region of recognition processes, has been described (Zatorre and Jones-Gotman 1991; Zatorre et al. 1992).

Conclusion
In summary, we found significant changes of olfactory functions in CD patients. Shorter H2S latencies occurred in objective olfactory testing. One possible explanation of this phenomenon could be a higher sensitivity and earlier recognition of H2S due to preexposure to H2S during the course of the disease. The lower amplitudes of event-related potentials following stimulation with olfactory and trigeminal stimulants demonstrate that hypoexcitability for chemical stimuli occurs in both sensory systems in CD patients.

In subjective olfactory testing, CD patients showed increased pleasant olfactory hedonic judgment. This could be interpreted as a natural counter regulation against malnutrition.

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Conflict of Interest

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