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The Influence of Semantic Processing on Odor Identification Ability in Schizophrenia

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Abstract

Despite the well-documented observation of odor identification deficits in schizophrenia, less is known about where the disruption in the process of correctly identifying an odor occurs. This study aimed to determine the potential moderating effects of semantic processing on the observed olfactory dysfunction in schizophrenia. Schizophrenia patients and healthy comparison subjects completed two versions of the University of Pennsylvania Smell Identification Test (UPSIT): an uncued free-response version and the standard multiple-choice paradigm, as well as three semantic measures: The Boston Naming Test, Animal Naming, and Pyramids and Palm Tree Test. Schizophrenia patients yielded significantly lower scores than the comparison group on the standard UPSIT and on semantic measures. No relationship was observed between olfactory and semantic task performance in patients. These data suggest that odor identification deficits may not be primarily due to semantic processing deficits in schizophrenia.

Keywords: Schizophrenia; Semantic processing; Olfactory; Olfaction; Smell; Boston naming test

Introduction

It is now widely accepted that individuals with schizophrenia have robust deficits in odor identification ability (Brewer et al., 2001; Goudsmit et al., 2004; Houlihan, Flaum, Arnold, Keshavan, & Alliger, 1994; Kohler et al., 2001; Kopala, Good, Martzke, & Hurwitz, 1995; Malaspina et al., 2002, 1994; Moberg et al., 1997; Stedman & Clair, 1998) that are stable and relatively unaffected by acute symptomatology, medication use, sex, or smoking status (for a review, *see* Moberg et al., 1999). Deficits in odor identification have also been observed during the first episode of psychosis (Kopala, Clark, & Hurwitz, 1993), in unaffected monozygotic twins of individuals with schizophrenia (Kopala, Good, Torrey, & Honer, 1998; Ugur, Weisbrod, Franzek, Pfuller, & Sauer, 2005), and in individuals at ultra-high risk for developing schizophrenia (Brewer et al., 2003; Kamath et al., 2011; Woodberry et al., 2010), raising the possibility that these deficits represent a biobehavioral marker of vulnerability for the illness.

Despite the well-documented observation of odor identification deficits in schizophrenia, less is known about where the disruption in the process of correctly identifying an odor occurs. Compared with other measures of olfactory performance, odor identification is considered a higher-order cognitive operation that requires more than just the ability to perceive odors (Hedner, Larsson, Arnold, Zucco, & Hummel, 2010). The process requires semantic knowledge or, more specifically, a previously learned inventory of recognized odors, the ability to retrieve this inventory, and the ability to associate a retrieved odor memory with a linguistic label. Thus, abnormalities at any level of semantic processing can disrupt task performance. Semantic

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processing is thought to influence odor identification performance, though the degree of influence can vary depending on the format of the odor identification task. Traditional odor identification tasks involve choosing the veridical semantic target among a set of foils. These choices are omitted if the test is administered in a free-response format. Studies have shown that healthy individuals have greater difficulty labeling odorants in the free-response format, exhibiting increased accuracy on forced-choice formats (Danthiir, Roberts, Pallier, & Stankov, 2001).

Prior research has suggested that more effortful processing is required when completing free odor identification tasks than cued, or multiple choice, odor identification tasks (Wehling, Nordin, Espeseth, Reinvang, & Lundervold, 2010). It has been theorized that a spontaneous identification format presents greater cognitive demands than the cued format, which relies primarily on sensory functions (Larsson, Finkel, & Pedersen, 2000; Larsson, Nilsson, Olofsson, & Nordin, 2004). Specifically, it is thought that cued odor identification tasks require far less effort in searching the semantic network than free odor identification tasks (Westervelt, Ruffolo, & Tremont, 2005). One study found statistically significant correlations between both cued and free odor identification tasks and neuropsychological measures such as the Digit Symbol Test and total learning and long delay free recall on the California Verbal Learning Test. However, importantly, associations between cognitive variables and these two olfactory task formats were stronger for the free odor identification condition (Wehling et al., 2010). Furthermore, another study found that while a measure of verbal knowledge independently contributed to odor identification performance, measures of executive functioning were unrelated, suggesting that similar cognitive abilities may underlie semantic processes and the ability to verbalize olfactory information (Larsson et al., 2004).

Similar studies have not been undertaken in schizophrenia samples but could be useful given that semantic deficits are consistently observed in patients. Impairments in semantic processing in schizophrenia are thought to arise from a reduced ability to retrieve and appropriately utilize semantic knowledge (Doughty, Done, Lawrence, Al-Mousawi, & Ashaye, 2008) and have been linked to impaired word-list generation, memory, organizational strategies, and information processing (Brebion, David, Jones, & Pilowsky, 2004; Doughty & Done, 2009; Marvel, Schwartz, & Isaacs, 2004). In addition, the reduced ability to form semantic associations in schizophrenia has been attributed to an overly active semantic associative network, in which many simultaneously active associations produce inappropriate responses (Spitzer, 1997). Currently, it is unclear to what extent odor identification deficits in schizophrenia may be accounted for by underlying semantic impairments and to what extent they result from a deficient ability to perceive odors. To address this, we utilized both open-ended and multiple-choice odor identification tasks, as well as three independent measures of semantic processing, in an effort to examine the relative contributions of semantic and olfactory processing to observed odor identification deficits.

We hypothesize that patients will perform worse than comparison subjects on all olfactory and semantic tasks and that both patients and comparison subjects will perform worse on the free odor identification task than the multiple choice odor identification task. However, we expect that patients will demonstrate a greater disparity between olfactory task formats due to impaired semantic abilities. We further predict that semantic and odor identification performance will be correlated in both groups, indicating semantic contribution to olfactory abilities. A significant group difference in olfactory change scores (i.e., the difference between traditional and open-ended odor identification performance) or a significant association between olfactory and semantic task performance in the schizophrenia cohort would suggest that odor identification deficits reflect, at least in part, a disruption in retrieving and utilizing semantic knowledge. Conversely, non-significant associations between olfactory and semantic task performance may suggest that odor identification deficits in schizophrenia are not primarily driven by difficulties retrieving and processing semantic information.

Method

Participants

Sixteen outpatients (12 men and 4 women) who met Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria for schizophrenia and 16 healthy comparison subjects (13 men and 3 women) were recruited to the Schizophrenia Research Center (SRC) at the University of Pennsylvania Perelman School of Medicine in Philadelphia, PA. Participation was limited to individuals between the ages of 18 and 50. The range of 18–50 years was imposed to eliminate the potential influence of age-related cognitive decline and variability associated with testing adolescents and older adults. The patient group consisted of both medicated and non-medicated outpatients, all of whom had received treatment for schizophrenia. Following a complete written and verbal description of the study, written informed consent was obtained from all subjects prior to participation. Subjects underwent a comprehensive medical, neurologic, and psychiatric evaluation by research psychiatrists from the SRC. This included the Structured Clinical Interview for DSM-IV, Patient or Non-patient Edition (First, Gibbon, Spitzer, & Williams, 1997), a physical examination, and routine laboratory tests. Exclusion criteria included history of: (a) axis I psychiatric disorder (other than schizophrenia for patients); (b) electroconvulsive therapy; (c) neurologic

disorder (including tardive dyskinesia); (d) head trauma with loss of consciousness; (e) alcohol and other substance abuse (according to DSM-IV criteria; assessed by history from patient and family, review of records, and toxicology screening); (f) medical conditions that may alter cerebral functioning (assessed by examination and routine laboratory tests), including cardiac, endocrine, renal, and pulmonary disease, as well as hypertension (blood pressure >140/90 mmHg); (g) upper respiratory infection; or (h) other conditions known to affect olfactory functioning (e.g., nasal septal deviation). Comparison subjects were additionally excluded for an axis II diagnosis of schizotypal, schizoid, or paranoid personality disorder or any first-degree relative with a psychotic illness. Evaluation of patients included ratings on the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962), the Scales for Assessment of Negative Symptoms (Andreasen, 1983) and Positive Symptoms (Andreasen, 1984), and the Quality of Life Scale (QOLS; Heinrichs, Hanlon, & Carpenter, 1984) by raters trained to a criterion reliability of 0.90 (intraclass correlation).

Patients and comparison subjects did not differ by sex ($\chi^2 = 0.18$, $df = 1$, $p = .67$) or age ($F(1, 30) = 1.80$, $p = .19$), though they differed significantly with respect to ethnic background ($\chi^2 = 6.58$, $df = 2$, $p = .04$). Patients had significantly fewer years of education than comparison subjects ($F(1, 30) = 9.86$, $p < .01$). As the illness itself adversely impacts educational attainment (Resnick, 1992), differences in parental education levels were assessed. Groups did not differ significantly with respect to the parental education level, Wilks' lambda = 0.03 ($F(2, 26) = 444.33$, $p = .10$). There were significantly more smokers in the patient group compared with the comparison group ($\chi^2 = 9.33$, $df = 2$, $p = .01$). Patients also smoked more cigarettes per days (pack-days) compared with comparison subjects ($F(1, 30) = 6.91$, $p = .01$), but did not differ from comparison subjects with respect to pack-years—a measure of an individual's cumulative smoking over time ($F(1, 30) = 2.72$, $p = .11$). Demographic and illness characteristics of the sample are provided in Table 1.

Materials

Olfactory tasks

University of Pennsylvania Smell Identification Test. The University of Pennsylvania Smell Identification Test (UPSIT) is a standardized 40-item forced-choice test of odor identification (Doty, Shaman, & Dann, 1984). Each item has a scent stimulus embedded in a microencapsulated "scratch and sniff" strip located at the bottom of each page. The four answer choices are listed above the smell strip. The overall score of the UPSIT is the sum of all the correct responses, with a maximum score of 40. Information on the specific stimuli, as well as reliability and sensitivity of this test, is detailed elsewhere (Doty, Frye, & Agrawal, 1989; Doty et al., 1984).

Table 1. Demographic and clinical characteristics

Variable	Patient group ($n = 16$) (mean [*SD*] or *n*)	Comparison group ($n = 16$) (mean [*SD*] or *n*)
Age (years)	34.3 (7.95)	30.7 (7.06)
Sex (*n*)		
Men	12	13
Women	4	3
Ethnic group (*n*)*		
Caucasian	3	9
African American	13	6
Mixed	0	1
Education (years)*	11.8 (1.80)	14.0 (2.13)
Mother's education (years)	12.1 (1.88)	14.2 (3.01)
Father's education (years)	13.5 (2.20)	14.7 (3.51)
Pack-years	7.63 (10.6)	2.47 (6.60)
Pack-days*	0.49 (0.48)	0.12 (0.30)
Age of onset (years)	20.1 (5.47)	
Duration of illness (years)	13.9 (8.01)	
BPRS total score	33.7 (12.8)	
SANS total score	26.7 (13.8)	
SAPS total score	23.2 (20.9)	
QOLS total score	25.0 (11.3)	

Notes: BPRS = Brief Psychiatric Rating Scale (Overall & Gorham, 1962); SANS = Scale for the Assessment of Negative Symptoms (Andreasen, 1983); SAPS = Scale for the Assessment of Positive Symptoms (Andreasen, 1984); QOLS = Quality of Life Scale (Heinrichs et al., 1984).
*Significant group difference ($p = .01$).

Picture Identification Test. The Picture Identification Test (PIT; Vollmecke & Doty, 1985) is designed to screen for individuals with cognitive deficits that may confound a subject's UPSIT score. The test is identical in item composition and response characteristics to the UPSIT, but the participants are asked to identify line drawings instead of odors (e.g., a line drawing of a slice of pizza is presented for item #1, pizza, as opposed to a "scratch and sniff" strip).

Semantic Tasks

Boston Naming Test. The Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983) is a widely used test of visual confrontation naming. It is comprised of 60 line drawings, which the participant is asked to identify. Points are awarded for correct answers given independently or after stimulus cues. The score is the sum of all the correct answers, with a maximum score of 60.

Animal Naming Test. The Animal Naming Test (Morris et al., 1989) is a test of semantic word-list generation. Participants are instructed to name as many animals as possible in 60 s. Responses are recorded verbatim and the total score is derived from the total number of unique animals named.

Pyramids and Palm Tree Test. The Pyramids and Palm Tree Test (PPTT; Howard & Patterson, 1992) is a matching test of semantic accessibility. Participants are shown two pictures and must decide which picture most appropriately matches with a third picture (e.g., the participant must decide if a pine tree or a palm tree matches with a pyramid).

Procedure

All tests were administered by a trained technician. The UPSIT was administered twice: First as a free-response test and subsequently as the standard multiple-choice test with four options. During the free-response format, subjects were asked to identify the odors as precisely as possible, doing their best to identify and not describe the odor. The second administration was completed according to the standard UPSIT testing procedure. The tester scratched the strip, presented it to the participant to smell, and then recorded the subject's response. All 40 items were presented birhinally for both the free-response and multiple-choice formats.

Answers to the free-response UPSIT were categorized into three groups: Hits, near-misses, and far-misses. A "hit" was defined as a response which identified the odor precisely (e.g., "peanut" for item #40, peanut), a "near-miss" was a response determined to be similar in quality to the correct response (e.g., "strawberry" for item #30, watermelon), and a "far-miss" was recorded if the answer was determined to be dissimilar to the target response (e.g., "gasoline" for item #1, pizza). These three response categories were selected to capture a three-level hierarchy of information about the stimulus (Rabin & Cain, 1984). If a subject's initial response was too general to be objectively scored, he was prompted to "be more specific." Two prompts were allowed per trial. All responses were judged by two independent raters who resolved any disagreements about labeling by consensus. The intraclass correlation coefficient for ratings of response categories was .92. The free-response UPSIT was followed by the administration of the BNT, the Animal Naming Test, and the Pyramids and Palm Trees Test. The standard multiple-choice version of the UPSIT was then given, followed by the PIT (Table 2).

Table 2. Means and standard deviations of odor identification and semantic measures in patients and comparison subjects

Test	Patient group ($n = 16$) (mean [*SD*])	Comparison group ($n = 16$) (mean [*SD*])
Standard UPSIT*	28.8 (3.13)	31.4 (4.00)
Free-Response UPSIT Hits	6.31 (2.73)	8.13 (4.32)
Free-Response UPSIT Near-Misses	4.94 (2.54)	7.06 (4.02)
Free-Response UPSIT Hits + Near-Misses	11.3 (3.47)	15.2 (6.72)
Free-Response UPSIT Far-Misses	28.8 (3.47)	24.8 (6.72)
Free-Response UPSIT Misses	33.8 (2.82)	31.9 (4.32)
The Boston Naming Test*	47.8 (8.93)	54.3 (4.77)
Animal Naming Test*	17.9 (7.13)	23.8 (5.47)
Pyramids and Palm Trees Test*	46.4 (3.86)	49.5 (1.83)

*Groups showed a statistically significant difference, $p < .05$.

Statistical Analyses

A general linear model analysis of covariance (ANCOVA) was conducted to compare patients and comparison subjects on traditional UPSIT performance, with pack-days included as a covariate. An analysis of variance (ANOVA) was conducted to compare patient and comparison subject performance on all measures of semantic functioning. An ANCOVA was also conducted to assess group differences with regard to naming accuracy in the free-response version of the UPSIT, and further analysis of error types was included to compare types of errors made. Spearman correlations were calculated to determine associations between the standard UPSIT scores and scores on each semantics task as well as semantic task performance and both BPRS and QOLS scores. With regard to the free-response UPSIT, Spearman correlations were conducted for each response type (hits, near-misses, far-misses, and total misses) and each semantic task. Finally, Spearman correlations were applied to determine the relation between change scores (derived by calculating the difference between the free and standard UPSIT scores) and each semantic task. We consider this to be an exploratory analysis and, given the small sample sizes, we did not correct for multiple comparisons.

Results

Psychophysical and Neuropsychological Performance

Consistent with prior research, results of a general linear model ANCOVA (with pack-days included as a covariate) revealed that patients performed significantly worse than comparison subjects on the traditional UPSIT, $F(1, 29) = 5.39$, $p = .03$, partial $\eta^2 = 0.16$. Similarly, the ANOVA showed that patients performed worse on all measures of semantic functioning: the BNT, $F(1, 30) = 6.47$, $p = .02$, partial $\eta^2 = 0.18$; Animal Naming Test, $F(1, 30) = 6.83$, $p = .01$, partial $\eta^2 = 0.19$; and the PPTT, $F(1, 30) = 8.23$, $p = .01$, partial $\eta^2 = 0.22$. Patients and comparison subjects did not differ significantly on the PIT, $F(1, 30) = 1.36$, $p = .25$.

Free-Response of Odors

ANCOVA of naming accuracy in the free-response condition revealed no significant differences between patients and comparison subjects, $F(1, 29) = 1.40$, $p = .25$, partial $\eta^2 = 0.05$, with both groups providing veridical names for the target odors only 16%–20% of the time. Although groups did not differ with regard to naming accuracy (hits), analysis of error types revealed that patients and comparison subjects showed differences at the trend level for types of errors made. Patients

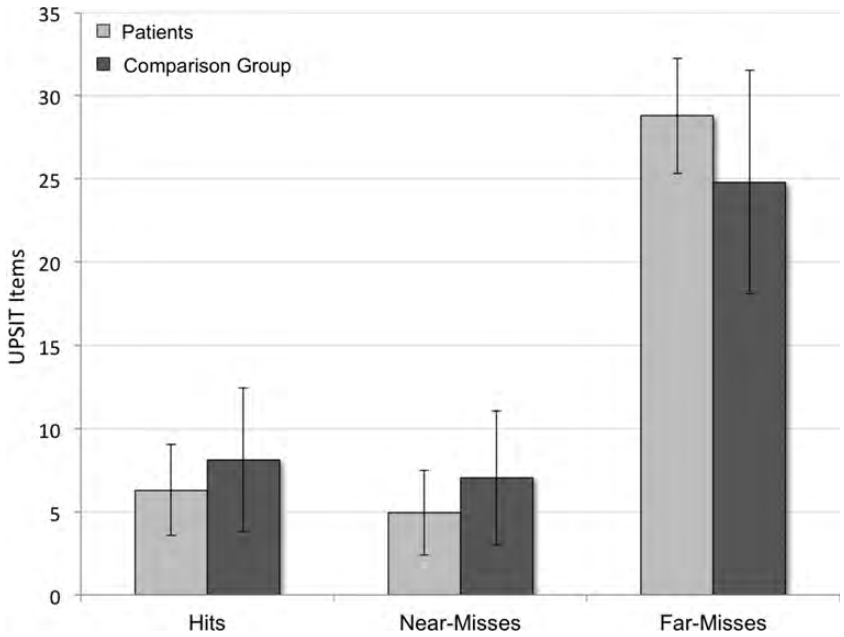

Fig. 1. Means and 95% confidence intervals for accuracy on the free-response UPSIT by group.

tended to make more far-miss errors, $F(1, 29) = 3.60$, $p = .07$, and fewer near-miss errors, $F(1, 29) = 3.10$, $p = .09$, than comparison subjects (Fig. 1). When hits and near-misses were combined into a single category describing general identification correctness, ANCOVA revealed that patients again perform worse at a trend level, $F(1, 29) = 3.63$, $p = .07$. An ANCOVA of group differences in UPSIT change scores (derived by calculating the difference between the free and the standard UPSIT scores) was not statistically significant, $F(1, 29) = 1.10$, $p = .30$.

Associations Between Olfactory Performance and Semantic Processing

Spearman correlations were used to compare the standard UPSIT scores for patients and comparison subjects to scores on each of the semantic tests. No significant correlations were found for patients between UPSIT scores and scores on the BNT ($r = .08$, $p = .78$), Animal Naming Test ($r = .06$, $p = .83$), or PPTT ($r = .06$, $p = .83$). Furthermore, patients' scores on these semantic tests did not correlate with their BPRS scores (all ps $> .45$) or their QOLS scores (all ps $> .61$). Comparison subjects' scores on the UPSIT did not correlate with their scores on the BNT ($r = .24$, $p = .38$) or the Animal Naming Test ($r = .09$, $p = .73$), though a positive association was observed between standard UPSIT and PPTT scores ($r = .50$, $p = .05$).

No relationships were found among either patients or comparison subjects between hits, near-misses, far-misses, or total misses on the free-response UPSIT and scores on the BNT, Animal Naming Test, or the Pyramids and Palm Trees Test (all ps $> .13$). Similarly, no relationships were observed between UPSIT change scores (derived by calculating the difference between the free and standard UPSIT scores) and semantic tasks in patients or in comparison subjects (all ps $> .23$).

Discussion

In the current study, healthy individuals and schizophrenia outpatients were assessed on free-response and multiple-choice versions of the UPSIT and on measures of semantic processing. Consistent with multiple prior studies (c.f., Malaspina et al., 2002), we found that patients scored significantly lower than comparison subjects on the standard UPSIT. Patients also showed significantly reduced verbal fluency and confrontation naming ability, which was consistent with results of a recent meta-analysis reporting large effect sizes for category fluency and naming impairment in schizophrenia (Doughty & Done, 2009). Though considerably fewer investigations have assessed semantic association ability in schizophrenia, moderate effect sizes have been reported for impairment on the PPTT and similar tasks. We similarly found that patients were impaired in their ability to correctly associate a semantic attribute to a target object on the PPTT, despite being able to correctly name objects in a multiple-choice format (PIT). Thus, the results of the current study replicate previous research indicating that patients have difficulty across multiple aspects of semantic ability.

On the open-ended UPSIT task, comparison subjects and patients showed equivalently poor performance, with 20% and 16% identification accuracy, respectively. These findings are similar to the results of Danthiir and colleagues (2001), who found that performance of healthy individuals on the UPSIT decreases significantly during the free response format. Although both groups had difficulty identifying odors without the provision of cues, patients tended to give answers that were more erroneous (far-misses) than comparison subjects. One possible explanation for this finding is that patients may rely on a more diffuse semantic network when attempting to name odors, which may result in an inability to generate categorically similar odor names during the free-response UPSIT. Alternatively, the greater incidence of far-miss errors in the schizophrenia group could be the result of poorer odor perception, in which the degraded sensory input leads to greater difficulty honing in on the correct verbal label. Nonetheless, this semantic burden appears to be substantially reduced during the standard UPSIT, which requires a more limited search of the semantic olfactory network to obtain a label for a particular odor. Congruent with this hypothesis, we found that the two groups benefitted similarly from the provision of odor tags, with patients and comparison subjects showing a 55.9% and 58.6% increase, respectively. In addition, intact picture identification scores and non-significant associations between scores on both conditions of the UPSIT and semantic measures were observed in the schizophrenia group. Taken together, these findings suggest that poor UPSIT performance in schizophrenia may represent an inability to identify odors that is not primarily due to generalized semantic processing dysfunction.

Several limitations should be noted. The current study used a small sample size of 16 patients and 16 comparison subjects, which may have limited the ability to detect statistically significant group differences, analyze sex differences, or eliminate trend relationships. Though we were able to replicate findings observed in previous studies, further examination in a larger sample of male and female patients is warranted. Future studies might also benefit from the inclusion of other measures of semantic and olfactory processing in order to examine the relative contribution of other types of olfactory and semantic abilities to odor identification in schizophrenia, particularly given the possibility that far-miss errors in schizophrenia may result from poorer odor perception. However, in general, findings on odor threshold deficits have been mixed (Moberg et al., 1999), and it has been suggested that odor detection abilities are not as reliant on higher-order processing as odor identification abilities

(Hedner et al., 2010; Westervelt et al., 2005), which is outside the scope of the current study. Finally, comparison subjects in the current study performed somewhat worse on the standard UPSIT than has been reported in previous papers (Kopala, Good, Morrison et al., 2001; Moberg et al., 2006). This may be a simple sampling artifact, with the observed group differences on the UPSIT being more robust if assessed in a different healthy comparison group. However, it is also possible that prior administration of the free response test had an unanticipated carryover effect that influenced comparison group performance on the subsequent standard UPSIT. Although we cannot prove or disprove this, it does not fundamentally alter the conclusions of the study.

In summary, patients demonstrated, as expected, performance deficits on the standard version of the UPSIT. In contrast, both schizophrenia patients and comparison subjects had difficulty choosing the correct odor label during the free-response UPSIT paradigm. When faced with the increased semantic burden of the free-response task, comparison subjects were better at generating odor labels within the correct semantic category, whereas patients tended to provide odor labels from unrelated semantic categories. The forced-choice UPSIT paradigm appears to eliminate a large portion of the semantic component present in the free-response paradigm by limiting semantic search requirements. Patients showed decreased identification accuracy on the standard UPSIT in contrast with the comparison group that was unrelated to semantic task performance. Overall, these findings suggest that odor identification difficulties experienced by patients are not directly related to observed semantic difficulties.

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Conflict of Interest

None declared.

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