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Reduced Olfactory Sensitivity, Discrimination, and Identification in Patients With Alcohol Dependence

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Background: Various olfactory deficits have been reported in the alcohol-induced amnestic syndrome (Korsakoff's syndrome). Less is known about olfactory functioning in nonamnesic and nondemented alcoholic patients.

Methods: Olfactory performance of 30 alcohol-dependent patients was assessed unirhinally using the Sniffin' Sticks (threshold, discrimination, identification, composite TDI score) and compared with that of 30 healthy controls, matched for sex, age, and smoking status.

Results: Patients showed significantly reduced olfactory sensitivity (higher threshold), discrimination, and identification compared with controls. No group differences were observed in laterality. Identification and discrimination group differences remained significant after controlling for differences in sensitivity. Olfactory deficits in patients were present independent of age, gender, and duration of abstinence (<3 months) and were not attributable to smoking or general cognitive abilities. More than half of the patients (56.7%) could be classified as hyposmic. Lower overall olfactory functioning (TDI) was associated with longer duration of a regular alcohol intake and higher values of γ-glutamyltransferase (GGT).

Conclusions: Olfactory dysfunction is common in nonamnesic and nondemented patients with alcohol dependence. Results suggest a detrimental effect of alcohol on central olfactory processing.

Key Words: Alcoholism, Olfactory Sensitivity, Olfactory Discrimination, Olfactory Identification, Unirhinal.

SEVERAL STUDIES HAVE shown that alcohol-induced amnestic disorder, commonly called Korsakoff's syndrome, is associated with olfactory deficits, namely dysfunctions in odor identification, discrimination, memory, sensitivity (threshold), and intensity (Doty et al., 1984; Gregson et al., 1981; Jones et al., 1975a,b; 1978; Mair et al., 1986; Potter and Butters 1979,1980).

It was suggested that alcohol abuse is associated with a modality-specific defect, which cannot be attributed to a general cognitive impairment or to the complexity of used tasks (Jones et al., 1975b,1978; Potter and Butters 1979). Olfactory deficits in Korsakoff's syndrome have been associated with CNS changes in diencephalic (thalamic/hypothalamic) and prefrontal (orbitofrontal) brain structures, both receiving input from the temporal lobe (Jones et al., 1975a,b; Potter and Butters, 1980). These brain areas are thought to play a major role in olfactory processing (Eslinger et al., 1982; Shipley and Ennis, 1996) and are associated with cognitive deficits in these patients (Fadda and Rossetti, 1998).

Several authors have proposed a continuum of alcohol-related cognitive deficits ranging from mild deficits (heavy social drinkers) to moderate (intermediate stage alcoholics) to severe deficits (Korsakoff's syndrome or alcoholic dementia) (Parsons, 1998; Parsons and Nixon, 1998; Ryback, 1971). Type and severity of brain damage linked to alcoholism are influenced by several factors such as drinking history, nutritional/vitamin deficiency, and genetic factors, and it is difficult to identify the exact pathogenetic mechanisms causing this damage. Whether women may have enhanced vulnerability of alcohol-related CNS complications is still under debate (Hommer et al., 2001; Mann et al., 1992; Pfefferbaum et al., 2001; Sullivan et al., 2002).

However, neuropathological and functional alterations in brain areas thought to be crucial in olfactory processing (diencephalic structures, temporal and prefrontal lobes), have also been observed in the brains of nonamnesic and nondemented alcoholics (Fadda and Rossetti, 1998; Jernigan et al., 1991; Moselhy et al., 2001).

To date there has been little systematic assessment of olfactory functioning in nonamnesic and nondemented al-

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coholics. A literature review of English-language studies of olfactory functioning in alcoholic patients, excluding studies without healthy control groups or sample sizes of <15, revealed only two studies (DiTraglia et al., 1991; Shear et al., 1992). Both studies demonstrated reduced odor identification ability [University of Pennsylvania Smell Identification Test (UPSIT); Doty et al., 1984] in male patients. As these findings were related to brain structures substantiated by MRI, the authors suggested that a peripheral contribution is unlikely to account for these relationships, and that olfactory loss in alcoholic patients may be mediated by cortical and subcortical structures, with the volume of the thalamus being a unique predictor of identification performance (Shear et al., 1992).

As mentioned by Martzke et al. (1997), the interpretation of data pertaining to more "secondary" or "higher order" olfactory processing (e.g., identification) is only possible within the context of available data about the integrity of the "primary" sensory systems (e.g., intact sensitivity), a premise routinely applied in other fields of neurobehavioral assessment. The characterization as primary and "secondary" olfactory measures just maintains an appreciation for the latter's ("higher order") dependence upon the former (lower order), without necessarily limiting the range of influence of central processes in all of them, including the threshold measure (sensitivity). From a neuropsychological point of view, and comparable with other sensory modalities (e.g., vision), it can be assumed that accurate identification ("higher order") requires intact sensitivity and quality discrimination (both "lower order"), and accurate quality discrimination itself ("higher order") requires intact sensitivity ("lower order") but not necessarily identification or naming of an odor.

Little is known about olfactory functioning in nonamnesic and nondemented alcoholic individuals other than identification, which has also been shown to be dysfunctional in a variety of other neuropsychiatric disorders (Duncan and Smith, 1995; Martzke et al., 1997), therefore assumed to be rather unspecific in terms of pathognomonic relevance.

Considering that one neuropsychological hypothesis in alcoholism (Parsons, 1998) states that the right hemisphere might be more vulnerable to alcohol-related effects ("right hemisphere" hypothesis), the olfactory system, with its pathways projecting predominantly ipsilaterally, provides a unique opportunity to probe for lateralized deficits. Deviations of patterns of olfactory laterality in patients may provide information of asymmetric neuropathology.

In summary, the present study was performed to replicate and extend prior research by exploring various olfactory domains unirhinally. The first aim was to replicate the findings of impaired olfactory identification in alcoholic patients (DiTraglia et al., 1991; Shear et al., 1992). Secondly, we hypothesized that nondemented and nonamnesic patients with alcohol dependence would demonstrate deficits in olfactory domains aside from identification. The third aim was to assess if the same patients showed abnormal patterns of olfactory laterality. Finally, we tested for possible alcohol-related gender differences in olfactory functioning. As recommended by Martzke et al. (1997), we also attempted to determine whether "higher order" processing deficits (e.g., identification, discrimination) exist independently of impaired "primary" ("lower order") functions (e.g., sensitivity).

METHODS

Subjects

Our sample included 30 alcohol-dependent patients and 30 healthy controls matched for sex, smoking status, and age. Demographic and clinical characteristics are presented in Table 1.

All patients participated in an inpatient treatment program at the Alcohol and Medication Abuse Unit of Innsbruck's Department of Psychiatry. Alcohol dependence was diagnosed following a semistructured interview based on DSM-IV and ICD-10 criteria and was confirmed with the Munich Alcoholism Test (MALT) (Feuerlein et al., 1980). Exclusion criteria were: (1) a history of an axis-I psychiatric disorder other alcohol dependence, nicotine, and/or caffeine abuse/dependence; (2) a history of neurological disorders or traumatic brain injury involving loss of consciousness; (3) serious medical disorders (other than a liver disease, three patients had a cirrhosis); and (4) other conditions known to affect cerebral and/or olfactory functioning (e.g., upper respiratory tract infection).

Medical history and drinking characteristics of patients were evaluated using a semistructured interview, supplemented by chart reviews and regular laboratory monitoring. Withdrawal-related symptoms were assessed using the modified Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-A) (Stuppaeck et al., 1994). Nineteen patients were completely free of psychotropic medication.

Potential control subjects, mainly recruited from hospital staff and by word of mouth, were not included if they had (1) a history of an axis-I psychiatric disorder other than nicotine and/or caffeine abuse/dependence (including a reported alcohol intake of more than 20 g of alcohol/day); (2) a family history (first degree) of mental disorder; as well as (3) a history of neurological, (4) medical, or (5) other conditions known to affect cerebral and/or olfactory functioning. The absence of exclusion criteria was determined by screening questionnaires and a semistructured clinical interview.

All subjects performed the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 1992), a screening instrument to identify persons whose alcohol consumption has become hazardous or harmful to their health. Each participant also completed a self-report measure of affective status, the Beck Depression Inventory (BDI) (Hautzinger et al., 1995). General mental abilities were assessed using the Mehrfachwahl-Wortschatz-Test (MWT-B) (Lehrl, 1995), a multiple-choice vocabulary test designed to measure premorbid (verbal) intelligence, and the Mini-Mental State Examination (MMSE) (Folstein et al., 1990), a brief screening instrument for cognitive impairment. Handedness preference was assessed using the Edinburgh Handedness Inventory (EHI) (Oldfield, 1971). Subjects with a laterality quotient >0.70 were classified as dextral. After a complete description of the study to the subjects, written informed consent was obtained prior to participation.

Procedures

Olfactory testing was performed by means of the Sniffin' Sticks (Hummel et al., 1997; Kobal et al., 2000). This test, based on pen-like odor-dispensing devices, comprises three domains of olfactory function, namely odor threshold (sensitivity), (quality) discrimination, and identification.

Thresholds for n-butanol (16 dilutions) were assessed using a single-staircase, triple-forced choice procedure. Three sticks were presented in random order, two containing the solvent and the third the odor at a certain dilution. The triplets were presented to the subjects until they had correctly discerned the odor in two successive trials, which triggered a

Table 1. Demographic and Clinical Characteristics

Variable	Patients			Controls			Analysis[a]		
	Mean	SD	N (%)	Mean	SD	N (%)	Value	*df*	*p*
Demographic variables									
Age[b]	45.8	9.3		45.3	8.7		$t = 0.187$	58	NS
Education (years)	9.5	1.6		10.0	2.5		$t = 0.851$	58	NS
Gender (female)			14 (47)			14 (47)		1	NS
EHI (dextral)			23 (77)			20 (67)		1	NS
Smoking characteristics									
Currently smoker (yes)			17 (57)			17 (57)		1	NS
Currently smoker (female/yes)			7 (23)			7 (23)		1	NS
Cigarettes (number/day)	27.1	12.8		14.1	4.4		$t = 3.959$	32	0.000
Duration of smoking (months)	305.7	90.7		273.5	102.4		$t = 0.968$	32	NS
Affective and neuropsychological measures									
Beck Depression Inventory (BDI)	12.3	9.3		3.5	3.5		$t = 4.892$	58	0.000
Mehrfachwahl Wortschatz Test (MWT-B)	28.5	3.6		27.6	3.0		$t = 1.016$	58	NS
Mini-Mental State Examination (MMSE)	28.3	1.9		28.5	1.2		$t = 0.575$	58	NS
Drinking characteristics									
Audit	27.1	5.6		2.5	1.5		$t = 23.176$	58	0.000
Age at first drink	15.8	4.5							
Duration									
-regular alcohol consumption (years)	19.4	9.5							
-alcohol dependence (years)	9.1	8.3							
Length of abstinence (days)[c]	35.9	36.6							
Alcohol intake (g/day) (last drinking month)[d]	209.0	108.2							
CIWA-A	15.2	4.6							
Gamma-glutamyl-transferase (GGT) (IU/l)	41.0	57.4							

[a] *t*-test, Fisher exact test; NS ($p > 0.05$).

[b] With the exception of a 7 year younger patient, age of matched pairs did not differ more than 4 years. Eighteen pairs had identical age or differed by 1 year, seven pairs differed by 2 years; patients' age range: 24–60; controls age range: 31–61.

[c] With one exception being sober for 150 days, period of abstinence prior to assessment ranged from 1 to 80 days.

[d] 13 patients were abstinent for more than 31 days.

reversal of the staircase. Threshold was defined as the mean of the last four out of seven staircase reversal points.

In the discrimination task, 16 triplets of sticks were presented in random order, with two containing the same odor and the third a different one. Subjects had to determine which of three odor-containing sticks smelled differently.

Identification was assessed by means of 16 common odors. Using a multiple forced-choice task format, identification of individual odors was performed from a list of four descriptors.

The sum of the results obtained for threshold, discrimination, and identification measures were presented as a composite TDI (Threshold Discrimination Identification) score. According to a multicenter investigation (Kobal et al., 2000), a TDI score less than 31 is considered "hyposmic," and a score of 15 is regarded as the cutoff value for "functional anosmia." Test and retest reliability and validity of the Sniffin' Sticks are well established; they have also been found to be suitable in the assessment of anosmia (Hummel et al., 1997; Kobal et al., 2000).

Olfactory measurements were performed separately for the left and right nostrils. For unirhinal presentation, a small piece of Microfoam tape (3M Health Care, St. Paul, MN) was fitted tightly over the borders of the opposing naris. The sequence of testing [first session: right nostril (R-L) or first session: left nostril (L-R)] was randomized and counterbalanced between groups. To prevent visual detection of the target sticks, subjects were blindfolded with nontransparent glasses during the threshold and discrimination tasks.

All subjects were told not to use perfume or perfumed cosmetics on the day of olfactory testing. They were also instructed neither to eat nor drink anything but water and to refrain from smoking at least one-half hour before commencement of testing. Testing took place in a calm, odorless, and well-ventilated room.

Affective and neuropsychological status evaluation in patients took place within a week of olfactory assessment, with 90% (neuropsychological measures) and 73.3% (affective measures) within 2 days. Controls performed all assessments on the same day.

Statistical Analysis

Group comparisons with respect to demographic and clinical characteristics were evaluated by *t* test or Fisher exact test. To test our hypotheses, data were analyzed by repeated-measures ANCOVA using the olfactory measures of interest (threshold, discrimination, identification, TDI) as dependent variables.

To check for possible effects of the test session (first versus second) on olfactory performance, e.g., due to possible attentional problems, repeated-measures ANCOVAs with the between-subjects factor *group*, the within-subjects factor *test session*, and *age* and *smoking* as covariates were performed. As these analyses did not show any significant effect of *test session*, all subsequent analyses were conducted without consideration of this variable.

To assess the main effects of group and the statistical interaction between group and tested nostril on olfactory performance, repeated-measures ANCOVAs with the between-subjects factor *group*, the within-subjects factor *side tested*, and *age* and *smoking* as covariates were performed. Subsequently, the variable *gender* and the *group by gender* interaction were added to the ANCOVA model.

Analyses of associations between olfactory performance (total scores) and affective and neuropsychological measures as well as drinking characteristics were evaluated using Pearson correlations.

Because the MMSE was associated with performance in discrimination and the TDI score in patients, the MMSE score was added to the set of covariates in the repeated-measures ANCOVAs, to control for this variable.

Finally, we studied whether deficits in "secondary" ("higher order") olfactory measures (e.g., identification, discrimination) are merely a consequence of "primary" ("lower order") olfactory deficits (e.g., threshold) or whether these deficits exist independently. Two types of analyses were performed (Martzke et al., 1997): (1) repeated-measures ANCOVAs (as discussed above) were performed using the "higher order" olfactory measure of interest as the dependent variable and included the score of the "lower order" measure as an additional covariate; (2) to illustrate the

Table 2. Olfactory Measures

	Left-side				Right-side				Analysis[a]					
	Patients (N = 30)		Controls (N = 30)		Patients (N = 30)		Controls (N = 30)		Group			Group × Side		
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Value	*df*	*p*	Value	*df*	*p*
Sniffin' Sticks														
Threshold (0–16)	6.6	2.8	8.4	3.0	6.2	3.3	8.0	2.5	F = 8.055	1,56	0.006	F = 0.014	1,56	NS
Discrimination (0–16)[b]	10.7	2.4	12.9	2.4	10.5	2.4	12.6	1.7	F = 18.810	1,56	0.000	F = 0.012	1,56	NS
Identification (0–16)	13.2	2.1	14.9	1.1	13.2	1.9	14.3	1.7	F = 11.344	1,56	0.001	F = 2.457	1,56	NS
TDI (0–48)[c]	30.4	4.9	36.1	5.2	29.8	5.3	34.9	3.9	F = 22.797	1,56	0.000	F = 0.240	1,56	NS

Note: Possible score ranges in parentheses.

[a] Repeated-measures analysis of covariance (between-subject factor "group," within-subject factor "side tested," and "age" and "smoking" as covariates); NS ($p > 0.05$).

[b] Main effect of gender [female means (SD): left = 12.6 (2.6); right = 12.3 (2.1); male means (SD): left = 11.1 (2.5); right = 10.9 (2.3); F = 8.095, df = 1, 54, p = 0.006].

[c] Main effect of gender [female means (SD): left = 34.7 (5.2); right = 33.5 (5.0); male means (SD): left = 32.0 (6.0); right = 31.4 (5.4); F = 4.574, df = 1, 54, p = 0.037].

results of the first analysis, a patient and a control subgroup, selected to obtain matched pairs with respect to the "lower order" olfactory measure, were formed and compared regarding the "higher order" olfactory measure by means of paired t tests.

Significance levels were $p < 0.05$ using 2-tailed tests.

RESULTS

Demographic and Clinical Characteristics

Patients and controls did not differ in terms of age, education, smoking status, duration of smoking, or neuropsychological measures (see Table 1). Patients smoked significantly more cigarettes per day, reported significantly more depressive symptomatology (BDI), and had higher scores in the AUDIT than controls. A separate group comparison of females and males yielded the same pattern of results.

No gender differences were observed within each group with the exception that female controls on average smoked significantly fewer cigarettes per day (mean, 11.4 ± 3.8) than male controls (mean, 16.0 ± 3.9; $t = -2.391$, $df = 15$, $p = 0.030$). Female and male patients were comparable in drinking characteristics, including age at first drink, duration of regular alcohol consumption, alcohol dependence and abstinence, alcohol intake (g/day) (last drinking month, last month, last year, and maximum amount), CIWA-A, and γ-glutamyltransferase (GGT) levels.

Olfactory Measures

As demonstrated in Table 2, alcohol-dependent patients showed significantly higher thresholds (lower sensitivity) and reduced discrimination and identification performance than controls. Composite TDI scores were significantly lower in patients compared with controls.

There was no significant main effect for *side tested* and no significant interaction effect between *group* and *side tested*. No significant effects were found for *age*, for *test session* (first versus second) and the interaction between *group* and *test session*, nor for sequence of testing (R-L versus L-R).

Means of the TDI total (left and right nostrils) revealed that 56.7% of patients and 13.3% of controls were classified as hyposmic (TDI < 31; $p = 0.001$). Similar frequencies of hyposmic patients were observed when analyzing the right and left nostrils separately (right, 56.7%; left, 53.3%). Additional analyses, classifying subjects according to unirhinal olfactory status (TDI: left < right or right < left), revealed no differences. Neither the comparison between groups nor a comparison within patients between normosmics and hyposmics revealed significant differences. None of the subjects fell below the cutoff value for anosmia (TDI = 15).

Effects of Gender

The *group by gender* analyses yielded no significant interaction effect in olfactory measures. Results indicate that females, irrespective of group, had higher discrimination and TDI scores compared with males (Table 2).

Effects of Smoking and Medication

ANCOVAs revealed no significant effect of *smoking*. The same applied when analyzing the patient group alone. Smoking and nonsmoking patients did not differ in the percentage of subjects classified as hyposmic (smokers, 58.8%; nonsmokers, 53.8%). Moreover, no significant relationships (Pearson r) between olfactory and smoking data (cigarettes per day, duration of smoking) were found in patients.

Repeated-measures ANCOVAs excluding patients with psychotropic medication ($n = 11$) did not lead to different results in olfactory measures than those found for the full sample, except that the threshold measure showed a trend toward lower sensitivity in patients ($F = 3.171$, $df = 1, 45$, $p = 0.082$). No significant differences in olfactory measures were observed between patients with and without psychotropic medication.

Effects of Affective and Neuropsychological Measures

Correlation analysis of affective (BDI) and neuropsychological (MWT-B, MMSE) measures with olfactory performance in patients revealed significant correlations only

between MMSE scores and discrimination performance ($r = 0.501$, $p = 0.005$) as well as TDI scores ($r = 0.370$, $p = 0.044$), indicating that patients with better MMSE performance showed better discrimination ability and higher TDI scores. However, addition of the variable MMSE as a covariate in the ANCOVAs demonstrated that the differences between groups in olfactory measures remained significant even after controlling for the MMSE score [threshold ($F = 7.583$, $df = 1, 55$, $p = 0.008$), discrimination ($F = 19.239$, $df = 1, 55$, $p = 0.000$), identification ($F = 10.812$, $df = 1, 55$, $p = 0.002$), and TDI ($F = 22.946$, $df = 1, 55$, $p = 0.000$)].

Relation to Drinking Characteristics

Correlation analysis of drinking characteristics [age at first drink, duration of regular alcohol consumption, alcohol dependence and abstinence, alcohol intake (g/day), (last drinking month, last month, last year, and maximum amount), CIWA-A, and GGT levels] with olfactory performance in patients revealed significant associations only between TDI scores and duration of regular alcohol consumption ($r = -0.375$, $p = 0.041$), as well as GGT values ($r = -0.376$, $p = 0.040$).

Controlling for Differences in Olfactory Measures

Repeated-measures ANCOVAs adding the olfactory variable to control for as a covariate demonstrated that the differences in discrimination and identification between groups remained significant even after controlling for differences in sensitivity (discrimination: $F = 12.469$, $df = 1, 55$, $p = 0.001$; identification: $F = 6.270$, $df = 1, 55$, $p = 0.015$), whereas the group difference in identification disappeared after controlling for differences in discrimination ($F = 2.722$, $df = 1, 55$, $p > 0.1$).

A second analysis was conducted by matching patients and controls either on threshold or on discrimination and then contrasting performance of matched pairs on subsequent olfactory measures. Of 17 pairs matched for threshold total scores (mean, 7.2 ± 1.8), threshold was identical in 9 matched pairs for each patient and control and 8 pairs differed by no more than $\pm$ 0.13. Matched-pair analyses revealed significant group differences between patients and controls matched on sensitivity in both discrimination ($t = 3.145$, $df = 16$, $p = 0.006$) and identification ($t = 2.757$, $df = 16$, $p = 0.014$). In the discrimination measure, 14 pairs could be matched with an identical discrimination total score (mean, 11.4 ± 1.5). Analyses revealed no significant group difference in identification between patients and controls matched for discrimination ($t = 0.549$, $df = 13$, $p = 0.592$).

DISCUSSION

The principal finding of the present study is that olfactory deficits do exist in nondemented and nonamnesic patients with alcohol dependence. More specifically, patients were impaired bilaterally in olfactory sensitivity (threshold), discrimination (quality), and identification when compared with healthy controls.

Our findings are in conflict with reports of alcoholic patients having intact or comparable olfactory performance to controls in identification (Kesslak et al., 1991; Mair et al., 1986; Serby et al., 1985) and threshold (Jones et al., 1975b,1978; Potter and Butters, 1979) but corroborate previous findings of impaired identification (DiTraglia et al., 1991; Shear et al., 1992) and discrimination (Potter and Butters, 1979). Methodological incongruities, including the lack of a healthy control group (Mair et al., 1986) or using unspecified nonalcoholic patients as controls (Jones et al., 1975a,b) as well as studying a variety of different olfactory tasks (Campbell and Gregson, 1972; Gregson et al., 1981; Kesslak et al., 1991) even in basically comparable olfactory domains (Jones et al., 1975b,1978; Potter and Butters, 1979; Serby et al., 1985), render comparison between previous reports and our study difficult. Furthermore, smaller sample sizes in all these investigations, which have mainly focused on Korsakoff's syndrome may, in part, account for some negative results with regard to the presence of olfactory deficits. Our finding of impaired identification confirms previous findings (DiTraglia et al., 1991; Shear et al., 1992) in male alcoholic patients ($n = 37$, 36 respectively) using the UPSIT.

Olfactory deficits in our patients were not attributable to psychotropic medication or smoking. Although patients smoked more than controls, none of the analyses in olfactory measures showed an effect of smoking. Furthermore, smoking and nonsmoking patients did not differ in any olfactory performance. In line with previous findings concerning odor identification (DiTraglia et al., 1991; Shear et al., 1992), we submit that it is unlikely that smoking alone can account for the observed deficits in patients.

With reference to cognitive functioning, it has to be stated that patients and controls did not differ in premorbid (verbal) intelligence (MWT-B) or the MMSE. And although overall olfactory functioning (TDI) and discrimination were positively correlated with MMSE performance in patients, more specific analyses controlling for the MMSE score suggest that general cognitive functioning cannot explain the observed olfactory deficits. Previous studies (DiTraglia et al., 1991; Shear et al., 1992) have also failed to find a correlation between cognitive and UPSIT performance in alcoholic patients. Furthermore, analyses with regard to test session indicated that olfactory deficits in patients were unlikely to reflect changes in performance due to attentional problems over time. There was also no association between olfactory performance and depressive symptomatology in patients.

The absence of any significant correlation of duration of abstinence prior to assessment or withdrawal symptom severity with olfactory performance suggests that minor symptoms which may persist after acute withdrawal had

little, if any, impact on olfactory performance in alcoholic patients. Moreover, results point to a relative independence of duration of abstinence, at least for a period of up to 3 months. DiTraglia et al. (1991) have also found no significant improvement of identification performance after 3 months of abstinence. The possibility of a chronic effect of long-term alcoholism on patients' olfactory functioning, which may lead to a slow and perhaps irreversible deterioration of olfaction (DiTraglia et al., 1991), needs to be further explored in future research.

Regarding potential sex differences of alcoholism (Hommer et al., 2001; Mann et al., 1992), our results do not provide evidence for sex differences or a disproportionate olfactory impairment in women (Pfefferbaum et al., 2001; Sullivan et al., 2002). An explanation may be the good comparability of female and male patients with respect to typical drinking characteristics in our sample. As this may also be the result of the small number of patients we studied, conclusions should be drawn carefully. Our finding that women in general can outperform men in olfaction is consistent with earlier research (Doty et al., 1984).

Reduced discrimination and identification in alcoholic subjects cannot be attributed to reduced sensitivity. Difficulties in identification seem to be linked to difficulties in discrimination of odors. In olfaction, as opposed to other senses, the relationship between quantity (sensitivity) and quality (discrimination) with subsequent identification is still unclear and even "peripheral" tasks such as threshold may involve higher cortical systems (Martzke et al., 1997). However, a potentially reduced sensory input due to a peripheral impairment, caused for instance by a trauma damaging the olfactory nerve, seems an unlikely explanation for the finding of reduced discrimination and identification. In such a case, one would expect an effect of sensitivity on these impairments, which we were able to rule out. In this context, our finding of a relative independence of discrimination deficits from sensitivity lends some support to the assumption that more central processing dysfunctions are responsible at least for "higher order" olfactory deficits in alcoholic subjects (DiTraglia et al., 1991; Shear et al., 1992).

Despite currently increasing knowledge in human processing of olfactory information (Brand et al., 2001; Sobel et al., 1998; Zald and Pardo, 2000), functional localization of olfactory functions has still not been resolved. Shear et al. (1992) have emphasized the importance of the thalamus in identification in alcoholic subjects. Our results indicate that identification deficits in alcohol-dependent patients might reflect dysfunctions in the ability to qualitatively discriminate between odors. Earlier research has already suggested that olfactory discrimination is processed mainly by the orbitofrontal cortex (Eslinger et al., 1982; Potter and Butters, 1980; Tanabe et al., 1975; Zatorre and Jones-Gotman, 1991) which receives projections either relayed through the mediodorsal thalamus (thalamo-cortical) or, as recently emphasized for discrimination function, directly via the temporal lobe (cortico-cortical pathways) (Hulshoff Pol et al., 2002; Savic et al., 1997). While there is strong evidence for frontal lobe pathology in alcoholism (Moselhy et al., 2001), its role in olfactory dysfunctions, specifically discrimination deficits, remains to be determined.

With regard to the "right hemisphere" hypothesis, olfactory deficits in our patients were found bilaterally without an indication for deviant laterality patterns. Our results, therefore, do not support this model (Parsons, 1998).

The significant relationships between overall olfactory performance (TDI) and duration of alcohol consumption on a regular basis, as well as GGT, is a strong indicator for an alcohol-related impairment. A recent finding, showing impaired olfactory functioning in patients with cirrhosis, independent of etiology and CHILD classification (Pabinger et al., 2000), also suggests a role of liver disease in olfactory impairments. Although GGT as a laboratory marker of poor liver function, as well as the role of liver disease in alcohol-related brain impairments in patients without cirrhosis, is still debated (Irwin et al., 1989; Walton and Bowden, 1997), our finding of lower overall olfactory functioning in patients with higher GGT points also to the need to further investigate these associations.

Over half (56.7%) of our patients were classified as hyposmic. Obviously this is discrepant to the 32.4% of alcoholic subjects found to be in the impaired range (UPSIT) by DiTraglia et al. (1991). Aside from using different olfactory tasks, DiTraglia et al. studied patients with a diagnosis of alcohol dependence or abuse while our study was restricted to patients with alcohol dependence. If there is a continuum of alcohol-related olfactory deterioration (Potter and Butters, 1979) as seen in neurocognitive impairments (Parsons, 1998; Parsons and Nixon, 1998), this might explain why we found a higher number of hyposmic patients.

The fact that more than half of our patients showed reduced olfactory functioning raises serious clinical concerns. Although less important in terms of communication and information exchange in humans, when compared with the visual and auditory system, the olfactory system has an important role as a warning device. Toxic leaking gas, poisonous fumes, the presence of fire and spoiled food, just to name a few, are health or safety hazards that can be detected through the sense of smell. Individuals with impaired olfactory functioning also have a significant impairment of their quality of life. An important issue in this context is food acceptance and pleasure. Although taste, detected solely by the tongue, contributes four basic sensations (sweet, sour, salty, bitter), the most important sensory component during eating and drinking is olfaction. This also leads to the question whether the well-known bad nutrition habits in alcoholic subjects may be, at least in part, related to olfactory deficits. To the best of our knowledge, this issue has not yet been studied.

The finding of impaired olfactory functioning also affects alcohol research using olfactory stimuli, mainly employed

in investigations of craving (e.g., Schneider et al., 2001). As alcoholic subjects have difficulties in identifying odors, and show dysfunctions in olfactory processing, results seem difficult to interpret.

Furthermore, our findings may have a bearing on olfactory research in general. Considering that sober "social" drinkers already manifest cognitive deficits (Parsons and Nixon, 1998), and assuming that alcohol-induced olfactory deficits parallel these impairments (Potter and Butters, 1979), a careful screening of alcohol consumption patterns of study samples in olfactory research become a crucial prerequisite. Drinking history should be addressed especially in research on certain neuropsychiatric disorders, which are often accompanied with alcohol abuse (e.g., schizophrenia) (Cuffel, 1992).

CONCLUSION

In conclusion, our findings of alcohol-related olfactory deficits support a dysfunction of more central olfactory processing mechanisms. As our neuropsychological measures only pertained to general mental abilities, the possibility of alcohol-related specific neurocognitive impairments accounting for these deficits cannot be excluded. In the search for explanations of olfactory deficits, our results also further emphasize the importance of addressing the role of liver dysfunction. The clinical relevance and consequences of our findings clearly warrant further exploration.

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