

## OLFACTORY FUNCTIONING IN PATIENTS WITH ALCOHOL DEPENDENCE: IMPAIRMENTS IN ODOR JUDGEMENTS

CLAUDIA I. RUPP,\* W. WOLFGANG FLEISCHHACKER, ARMAND HAUSMANN, DOLORES MAIR,  
HARTMANN HINTERHUBER and MARTIN KURZ

Department of Psychiatry, Medical University Innsbruck, Austria

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**Abstract** — **Aims:** Prior studies indicate that alcohol-dependent patients have impaired olfactory sensitivity, odor quality discrimination and identification ability. However, olfactory functioning with regard to the immediate, perception driven odor associations is unknown. Therefore, this study assessed olfactory judgements in nonamnestic and nondemented patients with alcohol dependence. **Methods:** Thirty alcohol-dependent patients and 30 healthy control subjects, well matched for gender, age and smoking status, and screened for olfactory sensitivity, were asked to rate intensity, familiarity, edibility and pleasantness of 16 odors using visual rating scales. **Results:** Compared with controls, patients showed lower scores in odor familiarity and impaired edibility judgements. These impairments were observed bilaterally, were present independently of age, gender, general mental abilities and length of abstinence, and not attributable to smoking or impaired olfactory sensitivity. No differences between groups were found in odor intensity and pleasantness judgements. **Conclusion:** These results extend prior findings of alcohol-related olfactory deficits, indicating impairments in olfactory processes of odor familiarity and edibility in alcohol-dependent patients. Although the basis of these deficits is still unknown, our finding of a distinct pattern of olfactory functional impairment, with spacing of perception of pleasantness and familiarity, suggests that there is no generalised olfactory impairment but that, neural olfactory networks may be affected differently.

### INTRODUCTION

There is increasing evidence that olfactory dysfunction is common in both patients with an alcohol-induced amnesic syndrome (Korsakoff's syndrome) (Jones *et al.*, 1975a,b, 1978; Potter and Butters, 1979, 1980; Doty *et al.*, 1984; Mair *et al.*, 1986) and in nondemented and nonamnestic alcohol disorders (Potter and Butters, 1979; DiTraglia *et al.*, 1991; Shear *et al.*, 1992; Rupp *et al.*, 2003). Previous studies have demonstrated that nondemented and nonamnestic patients with alcohol disorders have impairments in odor identification (DiTraglia *et al.*, 1991; Shear *et al.*, 1992; Rupp *et al.*, 2003), discrimination (Potter and Butters, 1979; Rupp *et al.*, 2003), and olfactory detection threshold sensitivity (Rupp *et al.*, 2003). Findings of our prior study (Rupp *et al.*, 2003) suggest that these deficits are alcohol-related, are independent of age, gender and depressive symptomatology, and are unlikely to be explained by effects of smoking or general mental abilities. In addition, results of this study showed that impairments in odor identification and discrimination are not attributable to impaired thresholds, a measure suggested to indicate potentially inadequate sensory input. Previous studies consistently suggest that alcohol-related olfactory deficits are resistant at least to early recovery after alcohol drinking cessation, and may reflect dysfunctions in central rather than peripheral mechanisms (DiTraglia *et al.*, 1991; Shear *et al.*, 1992; Rupp *et al.*, 2003).

Although brain regions closely associated with olfactory processing (Shipley and Ennis, 1996), such as diencephalic, medial-temporal and frontal brain areas, are commonly found

to show neuropathological and functional alterations in alcoholism (Fadda and Rossetti, 1998; Moselhy *et al.*, 2001), presently, the basis of alcohol-related olfactory deficits is unknown. A growing knowledge of deficits in olfactory processes associated with alcoholism seems of particular interest for several reasons. Aside from the fact that olfactory deficits have been suggested to represent early clinical signs with potential diagnostic utility in disorders such as Alzheimer's and Parkinson's disease (Doty, 2003; Hawkes, 2003), or schizophrenia (Rupp, 2003; Moberg and Turetsky, 2003), findings of alcohol-related olfactory deficits also have implications for alcohol research, particularly with regard to olfactory cue-induced alcohol craving research. Moreover, olfaction clearly serves several important and potentially even life-saving roles in day-to-day life, and the impact of the loss of olfactory function on safety, health and quality of life is frequently overlooked.

Olfactory perception and processing definitely have several additional dimensions than those thus far investigated in alcohol-dependent patients. Odors have the ability to elicit immediate perception driven associations, and humans can perform many olfactory functions including judgements of odors such as pleasantness, familiarity, intensity and edibility. Little is known about olfactory functioning in alcohol dependence with regard to these olfactory processes. Earlier studies have reported that alcoholic Korsakoff patients show an impairment in the scaling of odor intensity (Jones *et al.* 1975b, 1978). Although data of cortical olfactory processing are still inhomogeneous, neuroimaging studies in healthy individuals indicate that not only olfactory tasks (i.e. detection threshold, discrimination) but also odor stimulus features (i.e. intensity, pleasantness) may have dissociated neural substrate representations in the nervous system (Royet *et al.*, 1999, 2001a; Savic *et al.*, 2000; Zald and Pardo, 2000; Zatorre *et al.*, 2000; Brand *et al.*, 2001; Anderson *et al.*, 2003). Only recently have researchers begun to attend to such issues in clinical

\*Author to whom correspondence should be addressed at: Medical University Innsbruck, Department of Psychiatry, Anichstrasse 35, 6020 Innsbruck, Austria.  
Tel.: 43 (0) 512 548353; Fax: 43 (0) 512 548353 40;  
E-mail: claudia.rupp@uibk.ac.at

measurements of olfaction dysfunction in Alzheimer's disease (Royet *et al.*, 2001b), Parkinson's disease (Hudry *et al.*, 2003) and schizophrenia (Hudry *et al.*, 2002; Moberg *et al.*, 2003; Rupp, 2003; Rupp *et al.*, 2004a,b). Odor judgements such as intensity, familiarity, pleasantness and edibility are considered to represent different types of olfactory processing, and may be impaired differently. To our knowledge, these types of olfactory processing have not yet been studied in chronic alcoholism. The aim of the present study was to extend prior research by determining whether deficits in olfaction in alcohol dependence also pertain to processes of odor intensity, familiarity, edibility and pleasantness. Given the atypical anatomy of olfactory functioning, with primarily ipsilateral projections, we also sought to investigate potential abnormal lateralization in these types of olfactory processing by a unirhinal investigation.

## METHODS

### *Subjects*

The sample of 60 participants consisted of 14 female and 16 male alcohol-dependent patients recruited from the inpatient treatment program at the Alcohol and Medication Abuse Treatment Unit of Innsbruck's Department of Psychiatry, and 30 healthy controls without a family history of mental disorder and well matched for gender (14 females) and smoking status (17 smokers). Diagnosis of alcohol dependence was determined by a semistructured interview based on DSM-IV and ICD-10 criteria and confirmed with the Munich Alcoholism Test (MALT) (Feuerlein *et al.*, 1980). Patients and controls were subjects of a previous report; characteristics of participants and methods have been described in detail (Rupp *et al.*, 2003). Briefly, patients and controls were not included or excluded for the following reasons: (i) history of an axis-I psychiatric disorder (including a reported alcohol intake of more than 20 g of alcohol/day for controls) other than nicotine and/or caffeine abuse/dependence, and alcohol dependence for the patient group; (ii) a history of neurological disorders or traumatic brain injury involving loss of consciousness; (iii) serious medical disorders (other than liver disease: three patients suffered from cirrhosis); and (iv) other conditions known to affect cerebral and/or olfactory functioning (i.e. upper respiratory tract infection). After a complete description of the study to the subjects, written informed consent was obtained prior to participation. This study was approved by the ethics committee of the Medical University Innsbruck.

Subjects were between 24 and 61 years of age (patients:  $45.8 \pm 9.3$ ; controls:  $45.3 \pm 8.7$ ). Patients and controls were also comparable in years of education (patients:  $9.5 \pm 1.6$ ; controls:  $10.0 \pm 2.5$ ), hand preference (EHI) (Oldfield, 1971) (dextral: 77% patients; 67% controls) and in general mental abilities such as (premorbid) intelligence (Mehrfachwahl-Wortschatz-Test) (MWT-B) (Lehrl, 1995) (patients:  $106 \pm 13$ ; controls:  $102 \pm 8$ ) and performance in the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1990) (patients:  $28.3 \pm 1.9$ ; controls:  $28.5 \pm 1.2$ ) (*t*-test; all *P*-values  $>0.05$ ). Patients reported more depressive symptomatology on the Beck Depression Inventory (BDI) (Hautzinger *et al.*, 1995) (patients:  $12.3 \pm 9.3$ ; controls:  $3.5 \pm 3.5$ ; *P*  $<0.001$ ).

The unirhinal screening for olfactory sensitivity showed that 60% of patients and 40% of controls had reduced left and/or right nostril sensitivity (threshold scores  $\leq 6$ ; Sniffin' Sticks; Hummel *et al.*, 1997; Kobal *et al.*, 2000).

Patients had a mean duration of regular alcohol consumption of  $19.4 \pm 9.5$  years and a mean history of  $9.1 \pm 8.3$  years of alcohol dependence. Eleven patients received psychotropic medication (i.e. antidepressants, anticonvulsants, anticraving drugs) at the time of testing. Mean length of abstinence at the time of olfactory assessment was  $35.9 \pm 36.6$  days. Nearly half of patients (*n* = 13) were abstinent for more than a month ( $>31$  days).

### *Olfactory measures*

To assess olfactory judgements, subjects were asked to rate intensity, edibility, familiarity and pleasantness of 16 odors on visual 7-point rating scales ranging from '0' (no smell) to '6' (extremely strong) and from '-3' (very - unedible, unfamiliar, unpleasant) to '+3' (very - edible, familiar, pleasant) respectively. Intensity judgements were performed using 16 stimuli of the Sniffin' Sticks test battery (identification task; Hummel *et al.*, 1997). Edibility, familiarity and pleasantness judgements were performed using 16 common everyday odors (real-world items). Half of the odors were edible (chocolate, mustard, coffee, cinnamon, peanuts, garlic, peppermint, beer), the other half unedible (cigarette butts, shampoo, glue, toothpaste, diesel, cleaner, pencil shavings, hand lotion). Everyday odors were changed regularly and presented in 250 ml polyethylene squeeze bottles with a flip-up spout, which for testing was equipped with an exchangeable hand-made Teflon nose-piece (Distel *et al.*, 1999; Rupp *et al.*, 2004a,b). To minimize visual, acoustic or proprioceptive cues, odors were secured in disposable coffeepot filter bags, which were suspended inside the bottles.

Means of the sum of single ratings were calculated. Edibility scores were analyzed as follows: the sum of edibility ratings of edible odors minus the sum of inedible ratings [ $(\sum \text{edible odors}) - (\sum \text{inedible odors})$ ].

To assess whether patients show abnormal patterns of laterality in these olfactory processes, olfactory judgements were performed separately for the left and right nostrils. For unirhinal presentation, a small piece of Microfoam™ tape (3 M 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.

### *Statistical analyses*

The comparison of performance in olfactory judgements (intensity, familiarity, edibility, pleasantness) between groups was performed by repeated-measures MANOVA with side (nostril) as the within-subjects factor and group as the between-subjects factor. Significant multivariate and interaction effects ( $p \leq 0.05$ ) were followed up by univariate contrasts. To control for potential effects of age or smoking, these variables were added as covariates (MANCOVA). Subsequently, the variable gender and the group by gender interaction were added to the MANCOVA model; only statistically significant covariates were kept in the model.

In addition, MANOVA's as described above were computed excluding patients with psychotropic medication. Performance

Table 1. Olfactory judgements

Variable	Patients				Controls				Analysis <sup>a</sup>					
	Left		Right		Left		Right		Group			Group × side		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	<i>F</i> value	df	<i>P</i>	<i>F</i> value	df	<i>P</i>
Manova overall <sup>b</sup>									<i>8.804</i>	<i>4,55</i>	<i>&lt;0.001</i>	<i>0.669</i>	<i>4,55</i>	<i>NS</i>
Intensity (0–6) <sup>b</sup>	3.4	0.7	3.3	0.7	3.6	0.5	3.4	0.7	1.101	1,58	NS	1.576	1,58	NS
Edibility (–48 – +48)	19.2	8.9	19.1	8.5	29.9	6.3	29.1	5.8	33.401	1,58	<0.001	0.272	1,58	NS
Familiarity (–3 – +3)	1.3	0.6	1.2	0.5	1.7	0.5	1.7	0.5	10.717	1,58	0.002	0.235	1,58	NS
Pleasantness (–3 – +3)	0.5	0.5	0.6	0.5	0.4	0.4	0.5	0.4	0.716	1,58	NS	0.063	1,58	NS

Note: possible score ranges in parentheses.

<sup>a</sup>MANOVA (printed in italics), followed by repeated measures ANOVA; NS (*P*-value > 0.5).

<sup>b</sup>Significant main effect of side (*F* = 2.791, *df* = 4,55, *P* < 0.05); main effect of side in intensity (left > right, *F* = 6.503, *df* = 1,58, *P* = 0.013).

in olfactory judgements was also compared between groups including subjects only with intact left and right olfactory sensitivity (left and right threshold scores >6; patients: *n* = 12; controls: *n* = 18). To determine whether performance in olfactory judgements depends on length of abstinence, MANOVA's as described above were performed within patients subdivided according to their length of abstinence (≤31 vs >31 days). Moreover, analyses of associations between performance in olfactory judgements (mean total scores) and clinical characteristics of patients such as general mental abilities (MWT-B, MMSE), depressive symptomatology (BDI), threshold scores, and length of abstinence were evaluated using Pearson correlations.

Additionally, the olfactory judgements of the alcoholic drink beer were analyzed separately by comparing (i) means of performance in edibility, familiarity and pleasantness judgements (repeated-measures ANOVA's), as well as (ii) correct edibility (edible: yes; scores >0), familiarity (familiar: yes; scores >0), and pleasantness judgements (pleasant: yes; scores >0) (Fisher's Exact Test).

## RESULTS

The MANOVA analyses of performance in olfactory judgements (intensity, edibility, familiarity, pleasantness) showed a significant main effect of group (Table 1). Results indicated lower familiarity and reduced performance in edibility judgements in patients compared with controls. There was a significant effect of side in intensity. However, no significant side-by-group interaction effect was observed. No significant effects were observed for age, smoking, gender and the gender-by-group interaction. Smoking and nonsmoking patients did not differ in olfactory judgement performance when analyzed separately.

The MANOVA analyses excluding patients with psychotropic medication did not yield different results in olfactory judgement measures than those found in the full sample. No group differences within patients were observed when comparing patients with and without psychotropic medication. Analyses restricted to subjects with intact olfactory threshold (scores >6) revealed the same pattern of results. Neither did olfactory judgements differ between patients subdivided according to the threshold score (≤6 vs >6)

nor was there a significant relationship (Pearson *r*) between olfactory judgements and thresholds in patients. Correlation analysis of affective (BDI) and general mental ability (MWT-B, MMSE) measures with performance in olfactory judgements in patients revealed no significant correlations. There was also no significant correlation between olfactory judgements and length of abstinence. No group differences within patients were observed when comparing patients according to length of abstinence (≤31 vs >31 days) (MANOVA).

Analyses of judgements of the olfactory stimulus of beer yielded a similar pattern of results. Repeated-measures ANOVA's revealed a significant effect of group in edibility judgements, indicating that patients were poorer in judging the odor of beer as something edible (drinkable) compared with controls (patients left:  $-0.1 \pm 1.8$ ; patients right:  $-0.4 \pm 1.9$ ; controls left:  $0.8 \pm 2.1$ ; controls right:  $1.1 \pm 1.9$ ; *P* = 0.012). While there was no significant difference between groups in pleasantness judgements, the analyses of familiarity judgements indicated a trend towards lower familiarity in patients (patients left:  $0.8 \pm 1.3$ , right:  $0.3 \pm 1.7$ ; controls left:  $1.3 \pm 1.4$ , right:  $1.0 \pm 1.5$ ; *P* < 0.1). There was a significant effect of side in familiarity judgements (left > right; *P* < 0.01). However, no significant side-by-group interaction was observed. Only 40% of patients compared to 67% of controls judged the odor of beer as being familiar with both sides (left and right nostril scores >0; *P* < 0.07) (scores ≤0: patients left: 47%, right: 47%). A correct judgement of the odor of beer as an edible item with both sides (left and right nostril scores >0) was only observed in five patients (17%) compared to 60% of controls (*P* = 0.001) (patients left: 33%, right: 37%; controls left: 60%, right: 70%). The number of subjects judging the odor of beer as pleasant (scores > 0) was small in both groups (patients left: 20%, right: 27%; controls both sides: 30%). The same results were obtained when analyses were restricted to former beer drinking patients (*n* = 21).

## DISCUSSION

The present study adds to the knowledge about the association between chronic alcoholism and olfactory dysfunctions. This is the first study that investigates olfactory intensity, familiarity, edibility and pleasantness judgements in alcohol

use disorders. It shows that familiarity and edibility judgements but not intensity and pleasantness judgements were affected in alcohol dependence. Patients showed lower scores in odor familiarity and performed more poorly in judging edibility of these odors when compared to healthy controls. In agreement with previous research in chronic alcoholism, which failed to observe a consistent lateralized deficit in cognitive domains (Sullivan *et al.*, 2000) and in olfactory functions such as sensitivity, discrimination and identification (Rupp *et al.*, 2003), there was no evidence for a lateralization of these effects. Our data indicate that impairments in familiarity and edibility judgements are present independent of age and gender, and are not attributable to psychotropic medication, smoking or impaired threshold, a measure suggested to indicate potentially inadequate sensory input. Performance in olfactory judgements in patients was also not related to general mental abilities, depressive symptomatology or length of abstinence. The finding that patients with shorter length of abstinence (<1 month) did not differ from patients with a longer length of abstinence (>1 month) suggests that these olfactory impairments may be resistant at least to early recovery after cessation of alcohol consumption. In addition to measuring olfactory sensitivity, discrimination and identification in alcohol dependence (Rupp *et al.*, 2003), we have now extended our research with regard to the functioning of odor judgments. Our present results indicate that next to deficits in olfactory sensitivity, discrimination and identification (Rupp *et al.*, 2003), olfactory impairments in alcohol dependence also include the processing of odor familiarity and edibility.

Given the reduction in olfactory sensitivity in patients with alcohol dependence when compared with healthy controls (Rupp *et al.*, 2003), it seems surprising that we could not observe a deficit in intensity judgement. A potential explanation may be that a sensitivity loss in alcohol-dependent patients is larger at weak concentrations, near the threshold level, but undetectable at clearly supra-threshold concentrations. Another explanation lies in the fact that perceived odor intensity and psychometric evaluation of sensitivity (detection threshold) are different measures, which are not necessarily concordant. Consistent with previous studies using a slightly different method for olfactory intensity measurements (Jones *et al.*, 1975b, 1978), our analyses demonstrate that intensity judgements of patients are comparable to controls, and that this is observed independently of reduced sensitivity.

Recently, Sobel *et al.* (2001) have reported that an impairment in sniffing contributes to olfactory impairment in Parkinson's disease. We submit that a sniffing impairment does not explain our findings. We observed both impaired (familiarity, edibility) and intact (intensity, pleasantness) olfactory functions in patients. An impairment due to sniffing most likely would have shown impairments in all olfactory functions, as, in fact, recently observed in Parkinson's disease (Hudry *et al.*, 2003).

It has been suggested that the process of olfactory identification includes different levels of analysis, with performance ranging from nonverbal feelings of familiarity to specific object names (Schab, 1991). Our findings of deficiencies in familiarity and edibility judgements in patients suggest impairments in olfactory processing that do not

necessarily require the knowledge of odor names or precise identification. In our previous study (Rupp *et al.*, 2003), we have found that impairments in odor identification in alcohol-dependent patients were no more apparent after controlling for impairments in nonverbal quality discrimination performance. In line with prior findings, the present data suggest olfactory dysfunctions in early stages of the process of higher-order odor identification in chronic alcoholism, including perceptual (familiarity) as well as semantic (edibility) odor representations (Royet *et al.*, 1999, 2001a,b).

Previous studies on olfactory dysfunction in neuropsychiatric disorders have reported impairments in all olfactory judgements in Parkinson's disease (Hudry *et al.*, 2003), in familiarity judgements in Alzheimer's disease (Royet *et al.*, 2001b), and in familiarity and edibility in schizophrenia, with some inhomogeneity in pleasantness judgements (Hudry *et al.*, 2002; Moberg *et al.*, 2003; Rupp *et al.*, 2004a,b). Thus, our findings in chronic alcoholism appear to resemble closest the findings in schizophrenia, a disorder also sharing a considerable overlap of brain abnormalities, for instance in the frontal and medial-temporal lobes (Shenton *et al.*, 2001; Rupp *et al.*, 2004b). Conclusions, however, about shared and differential deficits in olfactory functioning clearly need systematic comparison between the diseases, with special care for the common comorbidity of alcohol use disorders.

Earlier findings and the present study underscore that central rather than behavioral or peripheral mechanisms underlie the various dysfunctions of olfactory processing in chronic alcoholism. According to a PET study (Royet *et al.*, 2001a), all olfactory judgements are associated with prefrontal, namely right orbitofrontal cortex (OFC) functioning. From the finding that right OFC activity was highest during familiarity judgements, and left OFC activity was highest during pleasantness judgements, it was suggested that some aspects of odor processing in the OFC are lateralized (Zald and Pardo, 2000; Royet *et al.*, 2001a). The involvement of the amygdala in hedonic processing (Zald and Pardo, 2000) was recently reported to be associated with the dimension of intensity rather than with pleasantness (Anderson *et al.*, 2003). Given that we found no impairment in pleasantness and intensity judgements in patients, it could be speculated that the brain regions associated with these types of olfactory processing are spared from the toxic effects of chronic alcohol consumption. Functional neuroimaging has begun to detail the neural underpinnings of olfactory functioning in humans (Sobel *et al.*, 1998; Zald and Pardo, 2000; Brand *et al.* 2001). Studies in patients with alcohol use disorders will help to provide insights into the underlying neural correlates of alcohol-related olfactory dysfunctions.

It is now evident that alcoholism is associated with a wide variety of olfactory impairments. Olfactory dysfunction can seriously impair people in their day-to-day activities and occupation, increase their risk of injury or even death, and reduce their overall quality of life (Murphy, 1993; Schiffmann, 1997; Reiter and Costanzo, 2003). Deficits may not only reduce patients' enjoyment of foods, but may also place them at risk for long term nutritional or health sequelae. They can alter food choices and intake, resulting in weight loss, challenged immunity and impaired nutritional status. Given that such conditions are commonly observed in patients with

chronic alcoholism, future research is needed to investigate the functional impact of olfactory dysfunction in chronic alcoholism.

The finding of impaired odor familiarity and edibility judgements in alcohol-dependent patients strengthens our previous suggestion (Rupp *et al.*, 2003) that the use of olfactory cues in alcohol research, which are commonly used in alcohol craving research, may compromise the interpretation of psychometric as well as functional neuroimaging data. This notion is further reinforced by considering that for nearly half of the patients the odor of beer, presented without any other cue (e.g. visual), was not even a familiar odor. While pleasantness judgements were not observed to be different between patients and controls, only five patients judged the odor of beer as something edible with both nostrils. Future research using olfactory stimuli therefore needs to consider that patients with chronic alcoholism have various distinct deficits in olfactory processing and that neural olfactory networks may be compromised.

## REFERENCES

- Anderson, A. K., Christoff, K., Stappen, I., Panitz, D., Ghahremani, D. G., Glover, G., Gabrieli, J. D. E. and Sobel, N. (2003) Dissociated neural representations of intensity and valence in human olfaction. *Nature Neuroscience* **6**, 196–202.
- Brand, G., Millot, J. L. and Henquell, D. (2001) Complexity of olfactory lateralization processes revealed by functional imaging: A review. *Neuroscience and Biobehavioral Reviews* **25**, 159–166.
- DiTraglia, G. M., Press, D. S., Butters, N., Jernigan, T. L., Cermak, L. S., Velin, R. A., Shear, P. K., Irwin, M. and Schuckit, M. (1991) Assessment of olfactory deficits in detoxified alcoholics. *Alcohol* **8**, 109–115.
- Distel, H., Ayabe-Kanamura, S., Martínez-Gómez, M., Schicker, I., Kobayakawa, T., Saito, S. and Hudson, R. (1999) Perception of everyday odors—correlation between intensity, familiarity and strength of hedonic judgement. *Chemical Senses* **24**, 191–199.
- Doty, R. L., Shaman, P. and Dann, M. (1984) Development of the University of Pennsylvania Smell Identification Test: A standardized microencapsulated test of olfactory function. *Physiology & Behavior* **32**, 489–502.
- Doty, R. L. (2003) Odor perception in neurodegenerative diseases. In *Handbook of Olfaction and Gustation*, Doty, R. L. ed., pp. 479–501. Marcel Dekker, Inc., New York, Basel.
- Fadda, F. and Rossetti, Z. L. (1998) Chronic ethanol consumption: From neuroadaptation to neurodegeneration. *Progress in Neurobiology* **56**, 385–431.
- Feuerlein, W., Ringer, C., Küfner, H. and Antons, K. (1980) The Munich Alcoholism Test (MALT). *Currents in Alcoholism* **8**, 137–147.
- Folstein, M. F., Folstein, S. E. and McHugh, P. R. (1990) *Mini-Mental-Status Test (MMST)*. German Version from Kessler, J., Markowitsch, H. J., Denzler, P. Hogrefe-Verlag, Göttingen, Bern.
- Hautzinger, M., Bailer, M., Worall, H. and Keller, F. (1995) *Beck-Depressions-Inventar (BDI)*. 2nd ed. Huber, Bern, Göttingen, Toronto, Seattle.
- Hawkes, C. (2003) Olfaction in neurodegenerative disorder. *Movement Disorders* **18**, 364–372.
- Hudry, J., Saoud, M., d'Amato, T., Daléry, J. and Royet, J. P. (2002) Ratings of different olfactory judgements in schizophrenia. *Chemical Senses* **27**, 407–416.
- Hudry, J., Thobois, S., Broussolle, E., Adeleine, P. and Royet, J. P. (2003) Evidence for deficiencies in perceptual and semantic olfactory processes in Parkinson's disease. *Chemical Senses* **27**, 537–543.
- Hummel, T., Sekinger, B., Wolf, S. R., Pauli, E. and Kobal, G. (1997) 'Sniffin' Sticks': Olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chemical Senses* **22**, 39–52.
- Jones, B. P., Moskowitz, H. R. and Butters, N. (1975a) Olfactory discrimination in alcoholic Korsakoff patients. *Neuropsychologia* **13**, 173–179.
- Jones, B. P., Moskowitz, H. R., Butters, N. and Glosser, G. (1975b) Psychophysical scaling of olfactory, visual, and auditory stimuli by alcoholic Korsakoff patients. *Neuropsychologia* **13**, 387–393.
- Jones, B. P., Butters, N., Moskowitz, H. R. and Montgomery, K. (1978) Olfactory and gustatory capacities of alcoholic Korsakoff patients. *Neuropsychologia* **16**, 323–337.
- Kobal, G., Klimek, L., Wolfensberger, M., Gudziol, H., Temmel, A., Owen, C. M., Seeber, H., Pauli, E. and Hummel, T. (2000) Multicenter investigation of 1,036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. *European Archives of Oto-Rhino-Laryngology* **257**, 205–211.
- Lehrl, S. (1995) *Mehrfachwahl-Wortschatz-Intelligenztest: MWT-B*. 3rd ed. Perimed-spitta, Balingen.
- Mair, R. G., Doty, R. L., Kelly, K. M., Wilson, C. S., Langlais, P. J., McEntee, W. J. and Vollmecke, T. A. (1986) Multimodal sensory discrimination deficits in Korsakoff's psychosis. *Neuropsychologia* **24**, 831–839.
- Moberg, P. J. and Turetsky B. I. (2003) Scent of a disorder: Olfactory functioning in schizophrenia. *Current Psychiatry Reports* **5**, 311–319.
- Moberg, P. J., Arnold, S. E., Doty, R. L., Kohler, C., Kaness, S., Seigel, S., Gur, R. E. and Turetsky, B. I. (2003) Impairment of odor hedonics in men with schizophrenia. *American Journal of Psychiatry* **160**, 1784–1789.
- Moselhy, H. F., Georgiou, G. and Kahn, A. (2001) Frontal lobe changes in alcoholism: A review of the literature. *Alcohol and Alcoholism* **36**, 357–368.
- Murphy, C. (1993) Nutrition and chemosensory perception in the elderly. *Critical Reviews in Food Science and Nutrition* **33**, 3–15.
- Oldfield, R. C. (1971) The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia* **9**, 97–113.
- Potter, H. and Butters, N. (1979) Continuities in the olfactory deficits of chronic alcoholics and alcoholics with the Korsakoff syndrome. *Currents in Alcoholism* **7**, 261–271.
- Potter, H. and Butters, N. (1980) An assessment of olfactory deficits in patients with damage to prefrontal cortex. *Neuropsychologia* **18**, 621–628.
- Reiter, E. R. and Costanzo, R. M. (2003) The overlooked impact of olfactory loss: Safety, quality of life and disability issues. *ChemoSense* **6**, 2–4.
- Royet, J. P., Koenig, O., Gregoire, M. C. *et al.* (1999) Functional anatomy of perceptual and semantic processing for odors. *Journal of Cognitive Neuroscience* **11**, 94–109.
- Royet, J. P., Hudry, J., Zald, D. H., Godinot, D., Gregoire, M. C., Lavenne, F., Costes, N. and Holley, A. (2001a) Functional neuroanatomy of different olfactory judgements. *Neuroimage* **13**, 506–519.
- Royet, J. P., Croisile, B., Williamson-Vasta, R., Hibert, O., Serclerat, D. and Guerin, J. (2001b) Rating of different olfactory judgements in Alzheimer's disease. *Chemical Senses* **26**, 409–417.
- Rupp, C. I., Kurz, M., Kemmler, G., Mair, D., Hausmann, A., Hinterhuber, H. and Fleischhacker, W. W. (2003) Reduced olfactory sensitivity, discrimination, and identification in patients with alcohol dependence. *Alcoholism: Clinical and Experimental Research* **27**, 432–439.
- Rupp, C. I. (2003) Dysfunctions in olfactory processing in schizophrenia. *Current Opinion in Psychiatry* **16**, 181–185.
- Rupp, C. I., Fleischhacker, W. W., Kemmler, G., Oberbauer, H., Scholtz, A. W., Wanko, C. and Hinterhuber, H. (2004a) Various bilateral olfactory deficits in male patients with schizophrenia. *Schizophrenia Bulletin*, in press.
- Rupp, C. I., Fleischhacker, W. W., Kemmler, G. *et al.* (2004b) Olfactory functions and volumetric measures of orbitofrontal and limbic regions in schizophrenia. *Schizophrenia Research*, in press.
- Savic, I., Gulyas, B., Larsson, M. and Roland, P. (2000) Olfactory functions are mediated by parallel and hierarchical processing. *Neuron* **26**, 735–745.
- Schab, F. R. (1991) Odor memory: Taking stock. *Psychological Bulletin* **109**, 242–251.

- Schiffman, S. S. (1997) Taste and smell losses in normal aging and disease. *The Journal of the American Medical Association* **278**, 1357–1362.
- Shear, P. K., Butters, N., Jernigan, T. L., DiTraglia, G. M., Irwin, M., Schuckit, M. A. and Cermak, L. S. (1992) Olfactory loss in alcoholics: Correlations with cortical and subcortical MRI-indices. *Alcohol* **9**, 247–255.
- Shenton, M. E., Dickey, C. C., Frumin, M. and McCarley, R. W. (2001) A review of MRI findings in schizophrenia. *Schizophrenia Research* **49**, 1–52.
- Shipley, M. T. and Ennis, M. (1996) Functional organization of olfactory system. *Journal of Neurobiology* **30**, 123–176.
- Sobel, N., Prabhakaran, V., Desmond, J. E., Glover, G. H., Goode, R. L., Sullivan, E. V. and Gabrieli, J. D. E. (1998) Sniffing and smelling: Separate subsystems in the human olfactory cortex. *Nature* **392**, 282–286.
- Sobel, N., Thomason, M. E., Stappen, I., Tanner, C. M., Tetrud, J. W., Bower, J. M., Sullivan, E. V. and Gabrieli, J. D. E. (2001) An impairment in sniffing contributes to the olfactory impairment in Parkinson's disease. *Proceedings of the National Academy of Sciences* **98**, 4154–4159.
- Sullivan, E. V., Rosenbloom, M. J. and Pfefferbaum, A. (2000) Pattern of motor and cognitive deficits in detoxified alcoholic men. *Alcoholism: Clinical and Experimental Research* **24**, 611–621.
- Zald, D. H. and Pardo, J. V. (2000) Functional neuroimaging of the olfactory system in humans. *International Journal of Psychophysiology* **36**, 165–181.
- Zatorre, R. J., Jones-Gotman, M. and Rouby, C. (2000) Neural mechanisms involved in odor pleasantness and intensity judgments. *Neuroreport* **11**, 2711–2716.