Eur Arch Psychiatry Clin Neurosci (2005) 255 : 94–98 DOI 10.1007/s00406-004-0536-8

ORIGINAL PAPER

Tarik Ugur · Matthias Weisbrod · Ernst Franzek · Ute Pfüller · Heinrich Sauer

Olfactory impairment in monozygotic twins discordant for schizophrenia

Received: 31 March 2004 / Accepted: 15 June 2004 / Published online: 12 November 2004

Abstract *Objective* Several studies demonstrated olfactory dysfunction in patients with schizophrenia, some reported deficient olfaction in unaffected relatives of schizophrenics as well. This study differentially assessed olfactory acuity as well as smell identification and smell discrimination in monozygotic twins discordant for schizophrenia and healthy, monozygotic control twins, to determine the genetic basis of different olfactory modalities and their association to schizophrenia. *Method* The Sniffin'Sticks test, a comprehensive and standardized olfactory test, was employed to assess the olfactory function of 10 monozygotic twin pairs discordant for schizophrenia versus 10 age- and sex-matched healthy, monozygotic twin pairs. *Results* Olfaction of affected monozygotic twins was globally impaired. Partial olfactory impairment of their unaffected co-twins may point to a genetic cause of olfactory impairment in schizophrenia. The influence of genetic factors was most evident for olfactory acuity and least evident for smell identification. All olfactory functions declined with duration of illness. Side of stimulus presentation did not influence olfactory performance. *Conclusions* Genetic factors associated with olfactory dysfunction may contribute to schizophrenia. The degree of the genetic influence on olfaction depends on the olfactory domain under examination.

Key words olfaction · schizophrenia · genetic · twin study

Dr. med. T. Ugur (✉)
Klinik für Psychiatrie der Friedrich-Schiller-Universität
Philosophenweg 3
07740 Jena, Germany
Tel.: +49-3641/9323489
Fax: +49-3641/9323402
E-Mail: Tarik.Ugur@med.uni-jena.de

M. Weisbrod · U. Pfüller
Dept. of Psychiatry
University of Heidelberg, Germany

E. Franzek
Dept. of Psychiatry
Verslavingskliniek
Rotterdam Alexander, The Netherlands

H. Sauer
Dept. of Psychiatry
University of Jena, Germany

EAPCN 536

Introduction

The isolated failure of olfactory modalities like smell identification (SI) or smell discrimination (SD) can result from an impairment of contributing cognitive factors, i. e. olfactory memory or smell recognition. Olfactory acuity (OA) is seen as an intermediate olfactory domain involving nasal and central nervous structures. Accordingly, lesion and functional studies suggest that OA relies on the integrity of the temporal lobes [30], whereas SI and SD, which implicate wider cognitive functions, depend also on the orbitofrontal cortex and the dorsal medial nucleus of the thalamus [11, 28, 39]. Thus, there is a considerable overlap between brain areas involved in olfaction and those related to schizophrenia, and repeated studies demonstrated olfactory deficits in schizophrenic patients [22]. Since olfactory dysfunction impedes emotional adjustment and contributes to anhedonia and social disablement in schizophrenic patients [6, 19], impaired olfaction is of theoretical interest and of clinical relevance.

Olfactory functions underlie – at least in healthy men – genetic influences [31]. Converging evidence from family as well as twin studies [16, 17, 42] suggests that olfactory dysfunction was indicative of a genetic predisposition to psychosis. However, these findings did not necessarily reach significance and they were discrepant concerning the olfactory domain, which was associated with schizophrenia. Some researchers supported the view that SI deficits in the absence of elevated olfactory thresholds (OT) reflect a predisposition to psychosis [17], whereas others discard SI as an indicator modality and suggest a more prominent role of OA [42]. To our

knowledge SD was not yet considered in genetic studies of schizophrenics.

SI and OA deficits in psychometrically ascertained schizotypic men [23, 26], and, more specifically, in siblings of patients with schizophrenia who met criteria for schizotypic personality disorder [20] also point to the potential power of olfactory dysfunction to demarcate the schizophrenic spectrum. Given the differing anatomic loci of different olfactory modalities and the expected influence of laterality, a differential assessment of multiple olfactory modalities in schizophrenic patients and their siblings should elucidate functional disturbance and advance the understanding of the genetic basis of schizophrenia.

Twin studies provide a powerful tool to explore the genetic grounds of diseases. In the yet only twin study examining olfactory functions in schizophrenia 12 pairs of monozygotic twins (MzT) discordant for schizophrenia were assessed [16]. They had significantly lower scores on SI for the combined (affected and unaffected) discordant twin group and no difference between affected and unaffected discordant twins. Therefore, it was concluded that genetic factors associated with a SI deficit may contribute to schizophrenia. However, the comparison group consisted of sex- and age-matched singletons. Since twins are exposed to an increased risk for pregnancy and birth complications [27], it can not be excluded that lower SI scores in both the affected and the unaffected twins reflect obstetric complications rather than a genetically determined association between olfactory impairment and schizophrenia.

The present study sets out to confirm and extend previous findings. Olfactory functions and their associations to schizophrenia were assessed in 10 MzT pairs discordant for schizophrenia. To control for mere effects of twin pregnancy and twin birth, the control group in our study consists also of MzT.

This study employed a comprehensive olfactory test tool [12] for the assessment of SD, SI and OA. Since studies on patients with focal cerebral excisions [11] and patients with temporal lobe epilepsy [5, 13] revealed an advantage favoring the right hemisphere, a bilateral assessment was made for SI and OA.

Method

Ten pairs of MzT discordant for schizophrenia and ten healthy, age- and sex-matched MzT pairs participated in the study (for demographic data and psychopathological scores see Table 1). The affected twins of the discordant pairs fulfilled ICD-10 [43] criteria for schizophrenia (n = 7) or schizoaffective psychosis (n = 3). Only one of the 10 unaffected twins suffered from any psychiatric disease. This one cotwin fulfilled ICD-10 criteria of remitted bipolar disorder (F31.7); his index-brother was diagnosed with schizoaffective disorder, depressive type (F25.1). Six of the affected discordant twins were on antipsychotic medication with an average of 407 mg chlorpromazine equivalents (range: 0 to 2625) per day. As far as atypical antipsychotics were concerned four patients were on clozapine ranging from 124 to 225 mg per day, and one patient was on risperidone 6 mg/d in addi-

Table 1 Demographic data, psychopathological scores [mean ± SD] and number of smokers for affected and unaffected twins discordant for schizophrenia and healthy control twins

	Affected twins	Unaffected twins	Control twins
Age [years]	34.5±11.4	34.5±11.4	35.3±11.1
Education [years]	11.0±1.8	11.5±2.0	11.1±1.4
SANS	27.1±14.2	0.9±1.2	0.0±0.0
SAPS	18.4±14.8	1.1±2.3	0.0±0.0
BPRS	32.4±6.4	19.4±1.6	18.5±0.5
Smokers [n]	7	5	8

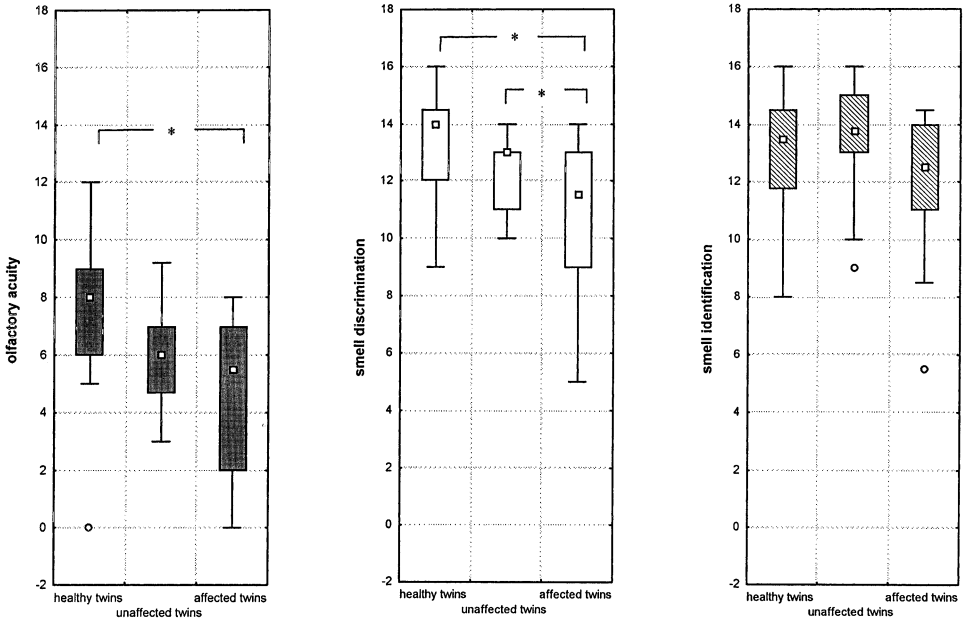

Fig. 1 Olfactory test scores [mean ± SD] of affected and unaffected twins discordant for schizophrenia and healthy control twins

tion to benperidole 14 mg/d. None of the co-twins took any psychoactive medication. Psychopathology was assessed using the Scale for the Assessment of Negative Symptoms (SANS) [1], the Scale for the Assessment of Positive Symptoms (SAPS) [2] and the Brief Psychiatric Rating Scale (BPRS) [24]. All twins were screened for systemic or neurological disorders, recent drug or alcohol abuse and history of neurological disorder and head injury. Control twins were free from mental retardation and from personal and familial histories of mental illness. The smoking history of all participants was recorded and they were divided into smokers versus non-smokers. Microsatellites were used in zygosity diagnosis of twins [4]. The study was approved by the ethics board of the University of Jena. After complete description of the study to the subjects, written informed consent was obtained from all participants.

Olfactory function was assessed with a commercially available comprehensively evaluated test battery, the Sniffin'Sticks test [12]. OA was determined with a series of smell sticks containing stepwise diluted n-butanol. SD required the recognition of an odor which was presented shortly before. SI was performed as a forced multiple choice test from a list of four descriptors, respectively. Smell sticks were randomly presented for 15 seconds in a standard environment by a trained rater. SI and OA were examined for each nostril separately. This was achieved by a mechanical occlusion of one nostril.

For statistical analyses multiple regression analysis was used. The initial analyses with multiple predictors considered group, age, smoking, gender, antipsychotics and side of stimulus presentation as factors. Further calculations included only factors which accounted for a significant amount of variance for any of the olfactory modalities (OA, SI, and SD). The significance level was set to $p < 0.05$ for all tests. The modified Wald-Test was applied to test all post hoc hypotheses. Multiple regression analysis requires by definition independence of observations. As MzT are not independent, this precondition is not fulfilled. This methodological flaw was overcome by assuming a multiple stage hierarchy of dependencies, taking MzT pairs as clusters in order to estimate variances of regression coefficients. The calculations were carried out with the svyreg (multiple regressions) and svytest (testing of hypotheses) components of the Stata statistical package [38].

Results

Smell test results are listed in Table 2. The initial analysis with multiple predictors identified group and age as relevant factors, whereas neither smoking, gender, antipsychotics nor side of stimulus presentation accounted for a significant amount of variance for any of the olfactory modalities (OA, SI, SD). Therefore, results presented are based on analyses conducted with the predictor variables group and age only. Multiple regression reached statistical significance for OA ($R^2 = 0.31$; $p = 0.014$), SD ($R^2 = 0.43$; $p < 0.001$), and SI ($R^2 = 0.43$; $p < 0.001$). The main group effect was significant for OA ($F\ [2/18] = 4.27$; $p = 0.030$) and SD ($F\ [2/18] = 4.63$; $p = 0.024$), whereas SI showed a trend ($F\ [2/18] = 3.02$; $p = 0.074$). Post hoc tests revealed that OA was significantly lower in affected than in healthy control twins ($F\ [1/19] = 9.00$; $p < 0.01$). There was a trend for unaffected twins to perform worse than control twins ($F\ [1/19] = 3.55$; $p = 0.075$). Unaffected twins performed somewhat better than affected twins but this difference fell short of significance ($F\ [1/19] = 2.84$; $p = 0.108$). SD was worse in affected compared to healthy control twins ($F\ [1/19] = 9.70$; $p < 0.01$) as well as compared to their unaffected co-twins ($F\ [1/19] = 5.01$; $p = 0.037$). Performance of unaffected twins was somewhat, but not significantly worse than that of healthy controls ($F\ [1/19] = 2.15$; $p = 0.159$). Since no significant group effect was found for SI no post hoc testing was performed. Furthermore, significant olfactory decline with age was found for SD ($F\ [1/19] = 13.67$; $p = 0.002$) and SI ($F\ [1/19] = 74.73$; $p < 0.001$). For OA the 5 %-criterium was shortly missed ($F\ [1/19] = 3.76$; $p = 0.068$).

Multiple regression performed on the affected twins alone revealed that only duration of illness had a significant impact on olfactory decline ($p < 0.05$ for all three olfactory modalities). In contrast, antipsychotic medication (chlorpromazine-equivalents) and psychopathology (SANS-, SAPS-, and BPRS-scores) did not correlate with any of the olfactory functions.

Table 2 Olfactory data [mean ± standard deviation] for affected and unaffected twins discordant for schizophrenia and healthy control twins

	Affected twins	Unaffected twins	Control twins
Olfactory acuity	4.7 ± 2.9	6.1 ± 2.0	7.7 ± 2.6
Smell identification	11.7 ± 2.8	13.3 ± 2.2	12.9 ± 2.2
Smell discrimination	10.8 ± 2.7	12.4 ± 1.3	13.3 ± 2.0

Discussion

The current twin study complements previous reports of olfactory dysfunction in schizophrenia. The twin design further allows the interpretation in a genetic versus environmental conceptual frame. In the following discussion, we first relate our results to previous findings of olfactory dysfunction in schizophrenia and, thereafter, discuss the implication for genetic matters:

In the sample of affected discordant twins OA was significantly diminished which is in line with results from some earlier studies [8, 10, 33, 40, 41], but contrasts other findings of intact OA in schizophrenic patients [3, 13, 15, 17]. However, the discrepant findings may also reflect the variety of substances and dilutions used across the studies. Dilutions of n-butanol, which were used in this study, proved to be appropriate to demonstrate the impairment of OA in schizophrenia. Nevertheless, the cause of impaired OA is not clear. Since intact or even enhanced OA was found in drug naive patients [15, 36], some authors attributed impaired OA in schizophrenic patients to long-term effects of neuroleptic treatment. However, there was no statistical hint that antipsychotics had an impact on OA within our study. In contrast, there were acuity deficits among unaffected twins, which have yet to be consolidated. If confirmed OA appears to be a basic deficit which does not depend on the manifestation of schizophrenia. In addition the question is not solved, whether the deficit is central or peripheral in origin. Commonly, OA is thought to rely on the integrity of olfactory epithelial receptors [18, 34]. However, detailed analysis of postmortem olfactory tissue did not reveal any differences between schizophrenic patients and

controls concerning the olfactory mucus membrane [37]. The discussion is further complicated by evidence for altered olfactory stimulus processing up to the cortical level [41].

Several studies reported impaired SI in schizophrenic patients [1, 9, 13, 16, 17, 21, 32], whereas group differences in our study only reached trend level. This is probably due to the SI test and the statistical procedure employed in the present study. Most previous studies on SI used the University of Pennsylvania Smell Identification Test (UPSIT) [1, 7, 9, 13, 16, 17, 21, 32]. Compared to the UPSIT the SI subtest of the Snifin' Sticks, which was employed in our study, implies a considerably smaller number of odors (16 compared to 40). Furthermore, a quite conservative statistical procedure was used in order to consider the dependence of MzT. Both the test and the statistical procedure may have lessened the differences between patients and controls with the result of a trend level finding.

SD, another domain, which demands the recognition of odors, was also quantified by forced choice test consisting of three choices (triplets). Active short-term memory is essential for SD. In this respect, SD differs from SI, which primarily relies on long-term olfactory memory. The diverging levels of significance between the SI versus SD tests may result from the different cognitive processes involved. These are short- versus long-term memory and passive versus active memory tasks. Insofar, our results point to a specific deficit in schizophrenics to actively establish and to maintain an olfactory memory trace for a short period of time. The finding also resembles working memory deficits which had been described as a core neuropsychological dysfunction in schizophrenia [35] and spatial working memory deficits attributed to disturbances prefrontal cortex [25]. Both deficits, spatial and olfactory working memory, might result from dysfunction in the same brain region. To our knowledge, there is no previous study which has attempted to correlate both findings yet.

Although test scores of unaffected twins narrowly missed significance, the fact that there remains a trend for a differential olfactory impairment should not be ignored. Concerning SD unaffected twins performed on the same level as healthy twins and better than their affected counterparts. In contrast, OA of unaffected twins was worse than the OA of control twins and not significantly different from their affected co-twins. Thus, it is suggested that genetic factors at least partially account for impaired OA in schizophrenic patients, whereas non-genetic factors have an impact on SD. Group differences were not evaluated concerning SI, since the factor group reached only trend level in the multiple regression analysis. Thus, so far current results support the conclusion of previous studies that olfactory dysfunction may be indicative of a genetic predisposition to schizophrenia [16, 17, 20]. However, impaired OA appears to precede the wider olfactory impairment, which is associated with the manifestation of schizophrenia. The comparison to healthy MzT also affirms the view that the deficits seen in the only previous twin study [16] were not due to the fact that the control group consisted of singletons who may have suffered from birth complications to a lesser extent than twins.

In a subgroup that comprised all twins diagnosed with schizophrenia, olfactory decline correlated with the duration of illness. Progressive decline of SI in schizophrenic patients has already been demonstrated in previous studies [15, 21]. Our results are in support of the findings on SI and suggest that it is also true for SD and OA. This implies that besides genetic also non-genetic factors further modulate olfactory functions in schizophrenic patients. However, an independent contribution of duration of illness could not be demonstrated conclusively, because the sample size was too small to partial out the age effect with a parametrical test.

In sum, the present study extends previous findings of olfactory dysfunction in schizophrenic patients, demonstrating SD and OA deficits in schizophrenic patients, and suggesting a core deficit of elevated OT, which appears to be genetically transmitted. The previous observation that SI declines with duration of illness is confirmed and extended to SD and OA. Impaired performance of unaffected discordant twins supports previous assumptions that genetic factors associated with olfactory dysfunction may be related to cerebral dysfunction present in schizophrenia. The current results further suggest that different smell tests vary in their sensitivity towards the genetic influence on olfactory decline and the Snifin'Sticks are a useful tool to explore olfactory dysfunction linked to schizophrenia. Nevertheless, our results suggest that detailed studies on the functional peculiarities and the cytoarchitecture of the olfactory system and the differential recording of specific olfactory dysfunctions in schizophrenic patients may shed light on the genetic basis and the functional processes involved in the manifestation and progression of schizophrenia.

Acknowledgements This work was supported by a grant (We 1996/1–3) from the German Research Community (Deutsche Forschungsgemeinschaft, DFG).

References

1. Andreasen NC (1983) Scale for the Assessment of Negative Symptoms (SANS). Iowa City, IA, University of Iowa
2. Andreasen NC (1984) Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, IA, University of Iowa
3. Bradley EA (1984) Olfactory acuity to a pheromonal substance and psychotic illness. Biol Psychiatry 19:899–905
4. Erdmann J, Noethen MM, Stratmann M, Fimmers R, Franzek E, Propping P (1993) The use of microsatellites in zygosity diagnosis of twins. Acta Genet Med Gemellol 42:45–51
5. Eskenazi B, Cain WS, Novelly RA, Mattson R (1986) Odor perception in temporal lobe epilepsy patients with and without temporal lobectomy. Neuropsychologia 24:553–562
6. Crespo-Facorro B, Paradiso S, Andreasen NC, O'Leary DS, Watkins GL, Ponto LL, Hichwa RD (2001) Neural mechanisms of anhedonia in schizophrenia: a PET study of response to unpleasant and pleasant odors. Jama 286:427–435

7. Doty RL, Shaman P, Dann M (1984) Development of the University of Pennsylvania Smell Identification Test. A standardized microencapsulated test of olfactory function. Physiolog Behav 32:489–502
8. Geddes J, Huws R, Pratt P (1991) Olfactory acuity in the positive and negative syndromes of schizophrenia. Biol Psychiatry 29: 774–778
9. Hurwitz TA, Kopala L, Clark C, Jones B (1988) Olfactory deficits in schizophrenia. Biol Psychiatry 23:123–128
10. Isseroff RG, Stoler M, Ophir C, Lancet D, Sirota P (1987) Olfactory sensitivity to androsterone in schizophrenic patients. Biol Psychiatry 22:922–925
11. Jones-Gotman M, Zatorre RJ (1988) Olfactory identification deficits in patients with focal cerebral excisions. Neuropychology 26:387–400
12. Kobal G, Hummel T, Sekinger B, Barz S, Roscher S, Wolf S (1996) "Sniffin' sticks": screening of olfactory performance. Rhinology 34:222–226
13. Kohler CG, Moberg PJ, Gur RE, O'Connor MJ, Sperling MR, Doty RL (2001) Olfactory dysfunction in schizophrenia and temporal lobe epilepsy. Neuropsychiatry Neuropsychol Behav Neurol 14: 83–88
14. Kopala L, Clark C (1990) Implications of olfactory agnosia for understanding sex differences in schizophrenia. Schizophr Bull 16:255–261
15. Kopala LC, Clark C, Hurwitz TA (1992) Olfactory deficits in neuroleptic naive patients with schizophrenia. Schizophr Res 8: 245–250
16. Kopala LC, Good KP, Torrey EF, Honer WG (1998) Olfactory dysfunction in monozygotic twins discordant for schizophrenia. Am J Psychiatry 155:134–136
17. Kopala LC, Good KP, Morrison K, Bassett AS, Alda M, Honer WG (2001) Impaired olfactory identification in relatives of patients with familial schizophrenia. Am J Psychiatry 158:1286–1290
18. Lancet D, Gross Isseroff R, Seidman LJ, Ben-Arie N (1993) Olfaction: from signal transduction and termination to human genome mapping. Chemical Senses 81:217–225
19. Malaspina D, Coleman E (2003) Olfaction and social drive in schizophrenia. Arch Gen Psychiatry 60:578–584
20. Moberg PJ, Doty RL, Mahr RN, Mesholam RI, Arnold SE, Turetsky BI, Gur RE (1997) Olfactory identification in elderly schizophrenia and Alzheimer's disease. Neurobiol Aging 18:163–167
21. Moberg PJ, Doty RL, Turetsky BI, Arnold SE, Mahr RN, Gur RC, Bilker W, Gur RE (1997) Olfactory identification deficits in schizophrenia: correlation with duration of illness. Am J Psychiatry 154:1016–1018
22. Moberg PJ, Agrin R, Gur RE, Gur RC, Turetsky BI, Doty RL (1999) Olfactory dysfunction in schizophrenia: a qualitative and quantitative review. Neuropsychopharmacology 21:325–340
23. Mohr C, Rohrenbach CM, Laska M, Brugger P (2001) Unilateral olfactory perception and magical ideation. Schizophr Res 47: 255–264
24. Overall JE, Gorham DR (1962) The brief psychiatric rating scale. Psychological Reports 19:799–812
25. Park S, Holzman P (1992) Schizophrenics show spatial working memory deficits. Arch Gen Psychiatry 49:975–982
26. Park S, Schoppe S (1997) Olfactory identification deficit in relation to schizotypy. Schizophr Res 26:191–197
27. Pernoll M (1991) Current obstetrics and gynaecology. Diagnosis and treatment. Prentice Hall, London
28. Potter H, Butters N (1980) An assessment of olfactory deficits in patients with damage to prefrontal cortex. Neuropsychologia 18: 621–628
29. Purdon SE (1998) Olfactory identification and Stroop interference converge in schizophrenia. J Psychiatry Neurosci 23: 163–171
30. Rausch R, Serafetinides EA (1975) Specific alterations of olfactory function in humans with temporal lobe lesions. Nature 255:557–558
31. Segal NL, Topolski TD, Wilson SM, Brown KW, Araki L (1995) Twin analysis of odor identification and perception. Physiol Behav 57:605–609
32. Seidman LJ, Talbot NL, Kalinowski AG, McCarley RW, Faraone SV, Kremen WS, Pepple JR, Tsuang MT (1992) Neuropsychological probes of fronto-limbic system dysfunction in schizophrenia. Olfactory identification and Wisconsin Card Sorting performance. Schizophr Res 6:55–65
33. Serby M, Larson P, Kalkstein D (1990) Olfactory sense in psychoses. Biol Psychiatry 28:829–830
34. Shepherd GM (1994) Discrimination of molecular signals by the olfactory receptor neuron. Neuron 13:771–790
35. Silver H, Feldmann P, Bilker W, Gur RC (2003) Working memory deficit as a core neuropsychological dysfunction in schizophrenia. Am J Psychiatry 160:1809–1816
36. Sirota P, Davidson B, Mosheva T, Benhatov R, Zohar J, Gross Isseroff R (1999) Increased olfactory sensitivity in first episode psychosis and the effect of neuroleptic treatment on olfactory sensitivity in schizophrenia. Psychiatry Res 86:143–153
37. Smutzer GS, Trojanowski JQ, Lee VM-Y, Arnold SE (1998) Human olfactory mucosa in schizophrenia. Ann Otol Rhinol Laryngol 107:349–355
38. Stata Corporation (1999) Stata Statistical Software: Release 6.0
39. Tanabe T, Yarita H, Ooshima Y, Takagi SF (1975) An olfactory projection area in orbitofrontal cortex of the monkey. Neuroscience 4:1269–1283
40. Turetzky BI, Moberg PJ, Yousem M, Doty RL, Arnold S, Gur RE (2000) Reduced olfactory bulb volume in patients with schizophrenia. Am J Psychiatry 157:828–830
41. Turetzky BI, Moberg PJ, Owzar K, Johnson SC, Doty RL, Gur RE (2003a) Physiologic impairment of olfactory stimulus processing in schizophrenia. Biological Psychiatry 53:403–411
42. Turetzky BI, Moberg PJ, Arnold SE, Doty RL, Gur RE (2003b) Low olfactory bulb volume in first-degree relatives of patients with schizophrenia. Am J Psychiatry 160:703–708
43. World Health Organization (1991) Tenth Revision of the International Classification of diseases. Clinical Descriptions and Diagnostic Guidelines. World Health Organization, pp 87–94