Olfactory Dysfunction in Patients With Head Trauma

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Background: The ability to smell is commonly altered by head trauma (HT). However, the nature, prevalence, prognosis, and etiology of such alterations are poorly understood.

Objectives: To quantitatively determine the degree of olfactory function in patients with HT-related chemosensory complaints and to examine the influences of age, sex, HT severity, time since HT, and other variables on such function. Also, to use quantitative magnetic resonance imaging (MRI) to establish whether and to what degree damage to the olfactory bulbs and tracts, frontal lobes, and temporal lobes occurs.

Patients and Methods: Two hundred sixty-eight patients with HT from the University of Pennsylvania Smell and Taste Center, Philadelphia, were administered a quantitative odor identification test, a depression inventory, and a medical history questionnaire; 66 were retested after individual test-retest periods ranging from 1 month to 13 years. The volume of olfactory-related brain structures was determined in 15 patients and 15 controls using MRI.

Conclusions: Patients complaining of HT-related olfactory dysfunction typically have anosmia and rarely regain normal olfactory ability, parosmia prevalence decreases over time in such patients, and damage to olfaction-related brain structures can be observed in most such patients using an appropriate MRI protocol.

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The sense of smell (cranial nerve 1) serves as an early warning system for the detection of smoke, toxic fumes, and spoiled foodstuffs and largely determines the flavor of foods and beverages. Unfortunately, this sense is seldom appreciated or adequately tested, even by neurologists, despite its significant contribution to quality of life and the fact that hundreds of thousands of patients present to medical practitioners each year with complaints of olfactory dysfunction. Such alterations can be of considerable consequence to patients, particularly to those whose livelihood or immediate safety depends on the ability to smell (eg, cooks, firefighters, plumbers, professional food and beverage tasters, employees of natural gas works, chemists, and numerous industrial workers). Among the more common causes of olfactory dysfunction is head trauma (HT). Head trauma–related olfactory disorders have been reported in the medical literature since the mid-1800s; however, even today data concerning the prevalence, prognosis, and etiology are found wanting. The first report of posttraumatic anosmia (loss of smell) in the modern literature is that of Jackson, published in 1864, who described a 50-year-old man who complained of loss of smell after falling off a horse. In 1870, Ogle concluded, on the basis of a study of 9 patients, that a blow to the occiput is more likely to produce anosmia than a hit to any other head region. In the same year, Nott's report that anosmia could occur in patients who do not lose consciousness. According to Costanzo and Becker, Legg provided, in 1873, the first description of HT-induced parosmia: a man fell off a cart and...
SUBJECTS AND METHODS

SUBJECTS

One hundred forty-eight men (mean [±SD] age, 40.4±16.2 years) and 120 women (mean [±SD] age, 42.3±17.8 years) who presented to the Center with complaints of olfactory dysfunction secondary to HT served as the primary study group. As shown in the Table, the causes of HT were diverse, although the majority were caused by vehicular crashes. Two hundred thirty-three patients were white, 20 were black, 9 were Hispanic, and 3 were Asian. The ethnic background of 3 patients was unknown. The patient population included 132 individuals with HT previously described in less detail in an earlier report.

One hundred sixty-nine patients provided information about the extracranial locus of injury, and 66 were retested on a second occasion to establish the stability of the dysfunction at individual test-retest intervals ranging from 0.5 to 13 years. The mean (±SD) ages of the 35 male and 31 female retest patients were 40.02±17.93 years and 50.36±16.57 years, respectively. The mean (±SD) ages of the 8 male and 7 female patients who underwent the olfactory system MRI evaluation were 36.63±11.80 and 38.71±4.89 years, respectively; those of the matched controls were essentially the same. The latter 2 groups met standard criteria necessary for MRI evaluation and comprised a subgroup of patients described in detail in another study.

METHODS

Olfactory Test Procedures and Collection of Demographic and Medical Information

All subjects were administered the University of Pennsylvania Smell Identification Test (UPSIT; commercially available as the Smell Identification Test, Sensonics Inc, Haddon Heights, NJ). This well-validated and highly reliable (test-retest r>0.90) 40-item "scratch and sniff" microencapsulated odorant test is sensitive to a wide range of smell deficits, correlates with other types of olfactory tests, including odor detection threshold tests, and is the most widely used olfactory test in North America.

On their initial visit to the center, each patient filled out a detailed questionnaire that included the BDI and basic medical and demographic information. For 50 of the 66 patients who were retested, a brief HT questionnaire was orally administered prior to a second administration of the UPSIT. Questions focused on the patients' perception of somatic and sensory changes since their trauma (including improvement or decline in olfactory function), additional information regarding the initial trauma (eg, duration of unconsciousness), and issues related to life adjustment. The BDI was also readministered at this time.

Magnetic Resonance Imaging

A 12.7-cm-round, general-purpose surface coil centered on the nasion was used to examine the olfactory bulbs and tracts of the MRI study group. Following a sagittal localizing scan, coronal images were acquired with 3-mm interleaved scans (repetition time, 500 milliseconds; echo time, 15 milliseconds; 2 excitations) and a 256x256 matrix with a 12-cm field of view. These scans were followed by 3-mm interleaved coronal fast spin-echo T2-weighted scans through the same anatomical structures (repetition time, 2000 milliseconds; echo time, 84 milliseconds; 2 excitations; 256x192 matrix). By using high-resolution surface coil imaging, the olfactory bulbs and tracts were readily localized, as was the entrance of the tracts into the brain near the septal nuclei. The head coil examination consisted of a sagittal localizing scan followed by a coronal T1-weighted scan (repetition time, 600 milliseconds; echo time, 11 milliseconds; 1 excitation) with 3-mm contiguous sections, a 25-cm field of view, and a 256x256 matrix through the temporal lobes. These scans were followed by 3-mm interleaved T2-weighted scans (repetition time, 3000 milliseconds; echo time, 90 milliseconds;
1 excitation) in the axial plane using a fast spin-echo technique through the entire brain. No contrast agents were used in the surface coil or head coil study.

Volumetric analysis was performed on a workstation (IGT Technologies, Toronto, Ontario) using the coronal T1-weighted scans. Such analyses were made of the left and right olfactory bulbs and tracts and the left and right temporal lobes by 2 independent evaluators based on tracing, thresholding, and 3-dimensional volumetric processing. Each olfactory bulb was identified at the anterior cribriform plate and each olfactory tract was identified as it extended posteriorly to enter the brain below the rostrum of the corpus callosum. As described elsewhere,\(^7\) the interobserver and intraobserver reliability is high in estimating the volume of these and other brain structures.

STATISTICAL ANALYSES

Standard parametric and nonparametric analyses were used (SYSTAT for Windows, SYSTAT Inc, Evanston, Ill). For example, frequency data were analyzed using a \(\chi^2\) test and overall differences among group means were evaluated using either analysis of variance or analysis of covariance (ANCOVA). Patient age was used as the primary covariate in most cases to mitigate the well-established association between age and olfactory function.\(^4\) Differences among specific group means were tested using contrasts that controlled for inflated \(\alpha\) levels caused by multiple comparisons. To establish associations among variables, Pearson correlation coefficients were computed with Bonferroni-corrected \(p\) values. The criterion for an individual test-retest change in an UPSIT or BDI score was that it fell outside a 95% confidence interval. For the UPSIT, this meant a change of 4 or more points; for the BDI, a change of 2.5 or more points.

For clarity of exposition, \(F\), \(df\), and \(\chi^2\) values are not cited in the text, only \(p\) values adjusted for covariates. In most cases, a \(p\) value refers to the significance of the \(F\) value of the implied main effect. In some cases, a description of the significant main effects and interactions is provided to convey the statistical effect. To emphasize the magnitude of correlations, \(r\) values are cited in the text. Raw means and associated SDs are presented and least-squares adjusted means are so indicated.

DEFINITIONS OF Olfactory FUNCTION AND DYSFUNCTION

The following definitions of olfactory function and dysfunction are used throughout. Anosmia indicates the total inability to smell (operationally defined as UPSIT scores >5 and <19); microsmia indicates a lessened ability to smell (operationally defined as UPSIT scores ranging from 19-33, inclusive, in men, and from 19-34, inclusive, in women); and normosmia indicates no meaningful olfactory loss (operationally defined as UPSIT scores \(\leq\)34 for men and \(\geq\)35 for women). Microsmia is broken down into the categories of mild microsmia (UPSIT scores of 30-33, inclusive, in men, and 31-34, inclusive, in women), moderate microsmia (UPSIT scores of 26-29, inclusive, in men, and 26-30, inclusive, in women), and severe microsmia (UPSIT scores of 19-25, inclusive, in men and women). The latter categories are akin to mild, moderate, and severe hearing loss in audition and are based on divisions of percentile ranks established for normative data from nearly 4000 subjects.\(^8\) Because of a sex difference in olfactory function on the UPSIT, separate norms are used for men and women; the aforementioned microsmia categories are adjusted for this difference.\(^9\) In a 40-item, 4-alternative, forced-choice test such as the UPSIT, scores of 5 and lower are highly unlikely in true anosmia and are considered to reflect probable malingering. No individuals were included in the study group whose scores were of this magnitude.

In this article, we use the term parosmia to describe all odor distortions, including odor phantoms, in place of the term dysosmia. The latter term has been used by some authors to signify both anosmia and distortions in olfactory function, and for this reason we have elected not to use this term here.

RESULTS

PROPORTION OF SAMPLE WITH LOSS OR DISTORTION OF Olfactory FUNCTION

One hundred seventy-nine (66.8%) of the 268 patients were found on initial testing to have anosmia. In addition, a 3-dimensional quantitative volumetric magnetic resonance imaging (MRI) analysis was performed on the olfactory bulbs/tracts, frontal lobes, and temporal lobes of 15 patients and 15 healthy controls matched for age, sex, and race to determine whether and to what degree these structures were grossly damaged by the HT.\(^19\)
Figure 1. Proportion of 268 patients with head trauma exhibiting various degrees of olfactory function and dysfunction, as defined by scores on the University of Pennsylvania Smell Identification Test.20

The mean (±SD) UPSIT scores of these 5 groups were as follows: 11.72±3.10, 21.59±1.76, 27.20±1.15, 31.63±1.41, and 36.44±2.18, respectively.

Ninety-four of the patients reported experiencing parosmia; for 27 men and 23 women (18.6%) this distortion was always present, and for 21 men and 23 women (16.42%) it was intermittent. Three men and 2 women (1.87%) stated that they had previously experienced a period when parosmia was present but no longer experienced the problem. One hundred fifty-seven patients (59%; 91 men and 66 women) reported never having a parosmic episode.

RELATIONSHIP OF AGE AND SEX TO DEGREE OF OLFACTORY LOSS

To determine whether patient age (either at time of trauma or at time of testing) or sex was associated with the degree of olfactory dysfunction, we first divided the total sample into 7 age categories corresponding to the time of trauma or time of testing (<21 years, 21-30 years, 31-40 years, 41-50 years, 51-60 years, 61-70 years, and 71-80 years) and performed an analysis of variance using the factors of age and sex on each of the 2 data sets. No meaningful main effects or interactions emerged (P>.50), indicating that olfactory test scores were not meaningfully related to patient sex or age at the time of trauma or the time of testing. Correlation coefficients computed between UPSIT data and patient ages at the time of trauma and at the time of testing did not reveal any meaningful associations, either in the total study group or in the male and female subgroups (P>.25). This lack of association between patient age and UPSIT score was also present after patients with anosmia (ie, those with UPSIT scores <19) were eliminated from the data set (P>.25).

To address the issue of whether one sex predominated in the anosmia, severe microsmia, moderate microsmia, mild microsmia, and normosmia categories, we performed a χ² analysis on the frequency data, by sex, across these categories. Because of low frequencies in the mild microsmia category, the mild microsmia and moderate microsmia categories were combined prior to analysis. No meaningful sex effects emerged from this analysis (P>.20).

RELATIONSHIP OF TEST SCORES TO PAROSMIA

To establish whether individuals with parosmia had less olfactory function than those without parosmia, we divided the entire study group (as well as the nonanosmic subgroup with UPSIT scores >18) into 4 categories: those who reported never experiencing parosmia, those who reported experiencing previous parosmia, those who were experiencing nontransient parosmia, and those who were experiencing transient (ie, on-off) episodes of parosmia. Since only 5 patients reported previous parosmia, this classification was dropped from the analysis. The data were subjected to an ANCOVA with parosmia group and sex as factors and age as the covariate. Results for the entire study group showed no significant parosmia group effect (mean [±SD] UPSIT scores: 17.19±10.07, 17.70±8.70, and 17.91±8.70, respectively; P>.90 for all comparisons). However, patients with some residual olfactory function (UPSIT scores >18) who had never experienced parosmia scored significantly higher on the UPSIT than those who were presently experiencing transient parosmia (Figure 2). In neither of these analyses was sex or its interaction with parosmia group significant (P>.40 for both).

INFLUENCE OF SITE OF INJURY ON OLFACTORY FUNCTION

Of 168 patients for whom explicit information regarding a single focus of impact was available, 61 (36.3%) received an injury to the front, 66 (39.3%) to the back, 17 (10.1%) to the right, 19 (11.3%) to the left, and 5 (3.0%) to the top of the head. The small number of individuals sustaining injuries to the top of the head precluded statistical use of these data. On average, blows to the back or side of the head produced slightly larger deficits in olfactory function than did blows to the front of the head (P<.03; mean [±SD] UPSIT scores: 15.38±7.96 for back of the head, 16.31±9.99 for side of the head, and 19.90±10.67 for front of the head; front vs back, P=.02; front vs side, P=.14; and side vs back, P=.94).
justed least-squares mean UPSIT scores: 22.85 \( [n=15]\), parosmia, and were currently experiencing transient parosmia. The statistical comparison of the test scores of patients never having parosmia to those of the combined nontransient and transient current parosmia groups was highly significant \( (P<.001)\).

RELATIONSHIP OF INDICES OF TRAUMA SEVERITY TO TEST SCORES

On the second test occasion, we obtained information likely associated with the severity of initial trauma, namely (1) the duration of unconsciousness and (2) the duration of the hospital stay. In the case of (1), we initially categorized the data into 3 loss-of-consciousness categories: none, up to 24 hours in duration, and 24 hours or longer in duration. An ANCOVA with loss of consciousness as a factor was performed on the UPSIT scores (with patient age as the covariate). No significant influence of the duration of loss of consciousness was observed \( (P=.95)\); least-squares adjusted mean UPSIT scores: 18.2, 18.0, and 16.8, respectively). However, when data only from patients with some olfactory function (ie, UPSIT scores >18) were subjected to this analysis, a significant influence was found \( (P=.04)\).

As shown in Figure 3, mean UPSIT scores of patients with loss of consciousness lasting 24 hours or longer were significantly lower than those of patients who had never lost consciousness and marginally lower than those of patients who had experienced loss of consciousness for less than 24 hours. An association between duration of loss of consciousness and UPSIT scores for the nonanosmic patient subgroup was also reflected by a significant correlation between these 2 measures \( (r=-0.56; P<.05)\).

An analogous ANCOVA was performed on the duration of hospitalization data for the entire retest group, as well as for the nonanosmic subgroup. The hospitalization duration data were divided into 3 categories: no hospitalization, 2 weeks or less hospitalization, and longer than 2 weeks hospitalization. As with the case of duration of consciousness, no significant influence of hospitalization duration was found when all of the retest UPSIT data were evaluated \( (P=.14)\), despite the fact that the mean UPSIT score of the nonhospitalized group was higher than the means of the 2 hospitalized groups \( (P=.98)\) (adjusted least-squares mean UPSIT scores: 22.85 \( [n=15]\), 16.72 \( [n=16]\), and 16.60 \( [n=18]\), respectively). However, in the nonanosmic subgroup a significant hospitalization duration factor was found \( (P=.003)\), reflecting higher UPSIT scores in those not hospitalized compared with those in the 2 hospitalization groups \( (mean\ UPSIT\ scores: 35.75 \ [n=7], 24.69 \ [n=6], and 29.12 \ [n=5], respectively; post hoc comparisons, \( P=.003\) and \( P=.06\), respectively). Unlike the variable of duration of unconsciousness, however, no meaningful correlation was found between UPSIT score and duration of hospitalization \( (r=-0.08; P=.76)\).

RELATIONSHIP OF TIME SINCE INJURY TO OLFACTORY TEST SCORES AND REPORTS OF PAROSMIA

The effect of time since injury on olfactory test scores was assessed in 2 ways. First, we computed Pearson correlation coefficients between time since injury and UPSIT scores for the entire group, as well as the nonanosmic subgroup (ie, UPSIT scores >18). In neither case was a significant relationship found \( (r=0.06\) and \( r=0.17; P=.28\) and \( P=.12\), respectively). Second, we computed ANCOVAs on the entire data set, as well as on the nonanosmic subset, with age as the covariate and sex and time since injury as the main factors. The time since injury factor was derived by dividing the data set into various consecutive periods of time since injury (eg, \( \leq 5.0\) months, \( 5.1-10.9\) months, \( 11.0-16.0\) months, \( 16.01-29.9\) months, \( 30.0-50.0\) months, and \( \geq 50.01\) months; \( 0-2.0\) years, \( 2.01-4.0\) years, \( 4.01-6.0\) years, and \( 6.01-8.0\) years). No significant difference in UPSIT scores among the time intervals was observed, either for the entire group or the nonanosmic subgroup, for any analysis \( (P>.50\) for all analyses). Thus, the length of time since a patient's head injury did not appear to be a meaningful determinant of the degree of olfactory dysfunction in this study group.

In contrast, when the parosmia data were divided into 2-year posttrauma intervals, the percentage of patients reporting parosmia (acute and transient combined) decreased from 42.1% to 15.5% over an 8-year period \( (P<.05\) by \( \chi^2\) test), with the major decrease occurring after 4 years (Figure 4). For the \( \chi^2\) calculation, the 4-to-6-year and 6-to-8-year category frequencies were combined to ensure adequate cell frequencies for a valid analysis.
Beck Depression Inventory scores were available for 229 (85%) of the 268 study participants. Using the diagnostic criteria of Beck et al., 4 (2%) of the 229 patients were severely depressed (BDI scores, 30-63), 21 (9%) were moderately to severely depressed (BDI scores, 19-29), and 71 (31%) were mildly to moderately depressed (BDI scores, 10-18). One hundred thirty-three individuals (58%) in the study group experienced little or no depression (BDI scores <10). Overall, no significant sex difference was observed in average BDI scores (male and female mean [±SD] BDI scores, 9.06±7.49 and 10.79±8.11, respectively; P=.25). However, following the combining of severe and moderate to severe BDI depression categories (because of a small number of individuals in the severe category), women tended to be more frequently represented than men in the moderate to severe depression category (15.38% vs 6.40%, respectively), as well as in the mild to moderate depression category (32.00% vs 29.81%, respectively), and less represented than men in the little or no depression category (54.81% vs 61.60%, respectively; P=.09 with the χ² test).

No association was found between the UPSIT score and the BDI score, either for the entire patient group (r=0.01; P=.88) or for the anosmic subgroup (r=-0.02; P=.89). Furthermore, no association was found, among those patients who were retested, between change in UPSIT score and change in BDI score between the 2 test occasions. This lack of association was observed in the whole group (r=-0.10; P=.51), in those patients who demonstrated significant UPSIT score changes across the 2 test occasions (r=-0.23; P=.34), in the anosmic subgroup (r=0.20; P=.44), and in patients without anosmia who demonstrated significant UPSIT score changes across the 2 test sessions (r=0.32; P=.34).

To determine if the BDI score was related to the presence of parosmia, we computed on the BDI scores an ANCOVA with sex and parosmia group (no present or previous parosmia, nontransient current parosmia, or transient current parosmia) as factors and age as the covariate. No significant differences emerged (P=.23). The same analysis performed on the anosmic subgroup also failed to reveal any influence of parosmia on depression (P=.44).

**POSTTRAUMATIC LONGITUDINAL CHANGES IN OLFATORY FUNCTION**

To determine whether UPSIT scores changed over time in the subgroup tested on the 2 posttrauma test occasions, we performed an ANCOVA with the main effects of test session and sex and the covariates of age, time between first and second test administrations, and time since injury. A significant interaction between test session and sex was found (P=.04), as well as a significant main effect of test session (P=.05). The interaction reflected a small increase in UPSIT scores between the 2 sessions for men (adjusted least-squares mean UPSIT scores, 17.45 and 20.87, respectively), but not for women (20.41 and 20.57, respectively).

As shown in Figure 5, nearly half of the retest group showed no change in condition between the first and second test sessions (mean [±SD] initial UPSIT score, 19.10±10.97; mean [±SD] follow-up UPSIT score, 19.73±10.73). Nearly one fifth of the patients scored worse on the second test occasion, moving from an average condition of severe microsmia to one of total anosmia (mean [±SD] initial UPSIT score, 20.08±8.82; mean [±SD] follow-up UPSIT score, 13.08±8.45). Slightly more than one third improved somewhat on retesting, moving, on average, from anosmia to a borderline moderate microsmic condition (mean [±SD] initial UPSIT score, 17.83±8.24; mean [±SD] follow-up UPSIT score, 25.46±8.62). No significant difference by sex was found in the relative frequency of men and women who showed increases, decreases, or no change between the 2 test sessions (P=.78 by χ² test).

The time between the 2 test sessions was not significantly different for patients whose UPSIT performances improved, worsened, or stayed the same (adjusted least-squares means: 58.97 months, 54.18 months, and 20.49 months, respectively; P=.34). Furthermore, no meaningful association was found between the amount of UPSIT score change across the test sessions and the time between the 2 sessions for the total study group (r=0.09), the subgroup that improved (r=-0.15), the sub-
group that worsened ($r=-0.14$), the combination of the latter 2 groups ($r=0.15$), and the group that did not significantly change ($r=0.37$; $P>0.15$ for all comparisons).

Initial UPSIT scores were not correlated with the amount of longitudinal change in UPSIT scores in either the patients whose olfactory ability improved or those whose olfactory ability declined between the 2 test sessions ($r=0.29$ and $r=0.20$, respectively; $P>0.35$ for both). Only 3 patients (5% of the study sample) had regained normal olfactory function on retesting; all 3 had moderate microsmia on initial testing and 2 were teenagers at the time of the injury. These patients included (at the time of retesting) a 28-year-old woman (initial UPSIT score, 26; follow-up UPSIT score, 36), a 29-year-old man (initial UPSIT score, 27; follow-up UPSIT score, 34), and a 59-year-old man (initial UPSIT score, 31; follow-up UPSIT score, 36). It is noteworthy that, in each of these patients, the time between the 2 test sessions was relatively long (ie, 10.75 years, 9.58 years, and 10.60 years, respectively).

A disparity was present between the subjective belief of many patients regarding their change in chemosensory function over time and the objective measure of such change. Although 11 of 51 patients for whom such data were available reported that, at the time of retesting, they believed they had regained olfactory function to some degree, statistically meaningful improvement (ie, test scores falling outside a 95% confidence interval) was found in only 7. The majority (ie, 38) of the study group reported no change. Of this majority, however, 11 showed actual improvement while 10 showed diminished olfactory function. Only 2 believed they had experienced a decline in olfactory function; in these 2 patients no statistically meaningful decline in UPSIT score was apparent.

**POSTTRAUMATIC LONGITUDINAL CHANGES IN DEPRESSION**

Of 52 patients who completed the BDI on the second test occasion, 19 scored the same as on their first evaluation, 19 scored lower, and 14 scored higher, as defined by scores falling outside a 95% confidence interval. No association was found between degree of change in depression and degree of change in olfactory test scores between the 2 test sessions ($r=-0.10$; $P=0.51$). When a correlation coefficient was computed for test scores only from individuals in whom statistically meaningful BDI changes occurred between the 2 test occasions, no significant association was found ($r=-0.17$; $P=0.35$).

**MRI FINDINGS**

The volumes of the left and right olfactory bulbs and tracts were lower in male patients with HT than in healthy matched controls (Figure 6). However, this was not the case for female patients with HT. The differential influence of HT on the olfactory bulbs/tracts of men vs women was reflected in a significant sex by group interaction term in ANCOVAs performed on the olfactory bulb/tract data (patient age served as covariate; $P<0.001$). The main effects of sex and olfactory bulb side, as well as the age covariate, were not significant ($P>0.10$ for all comparisons); however, the main effect of group was statistically significant ($P<0.001$). Multiple comparisons revealed that bulb/tract sizes in male patients with HT differed significantly ($P<0.001$) from those of all other groups, which did not differ significantly from one another. Thus, HT significantly altered olfactory bulb/tract size only in male patients. Similar analyses performed on temporal lobe volume data revealed no significant effects of trauma or its interaction with sex ($P>0.13$), implying that the volume of these relatively large structures was not meaningfully altered by trauma.

**COMMENT**

This study is the first large-scale analysis of olfactory function in patients with HT presenting to a specialized smell and taste disorder treatment center. Of 268 patients with HT presenting with complaints of olfactory disturbance, 234 (87.3%) were found to have demonstrable olfactory dysfunction, with 179 (66.8%) having anosmia and 55 (20.5%) having microsmia. These figures are in accord with earlier, less extensive studies on this topic that incorporated modern psychophysical testing. Thus, of 25 patients with HT evaluated by Costanzo et al., 15 (60%) were found to have anosmia, while 67% of 95 patients assessed by Moit and Leopold had anosmia. In the latter study, hyposmia was found in 23% of the cases, a number quite similar to the 21% found in the present work.

Using well-defined statistical criteria, 20 our study found that olfactory function in more than a third (36%) of the 66 retested patients with anosmia or microsmia improved over time, while that in nearly a fifth (18%) worsened. The proportion of patients showing improvement is essentially equivalent to the 35% improvement rate reported in a recent longitudinal study 17 of 20 patients with HT that incorporated the UPSIT and the 4-point change criterion of the current work. However, the degree of recovery was modest in the present study, with only 3 individuals recovering normal olfactory function (<5% of the patients). In these 3 patients, approximately 10 years intervened between the 2 longitudinal tests; in 2 the HT occurred early in life and in the remaining patient the amount of initial dysfunction was mar-
original. These findings, along with the observation of little meaningful longitudinal change and no strong association between olfactory test scores and time between test sessions, suggest that the prognosis for most patients with HT-related olfactory loss is poor.

Our observation that patients with olfactory loss secondary to HT only rarely regain normal olfactory function, a phenomenon alluded to by Duncan and Seiden,\(^\text{17}\) stands in sharp contrast to findings of earlier studies that either used no sensory testing or comparatively unsophisticated testing procedures. For example, Leigh\(^\text{9}\) reported in 1943 that 6 (8%) of 72 patients with anosmia recovered olfactory function, noting, “Refined methods of olfactometry were not employed, as an estimate was needed on the basis of a simple clinical test.” Sumner\(^\text{10}\) found, in his 1964 study of 87 putative cases of anosmia culled from a sample of 1167 patients with HT, “in over one-third of the patients who develop post-traumatic anosmia, recovery ultimately takes place.” It is not clear in this case what, if any, sensory testing procedure was used. As suggested by Sumner, some recovery of olfactory function was presumably due to regression of hematomas or reduction of nasal swelling, since many of these patients received their first olfactory test relatively soon after their HT. More recently, Zusho\(^\text{14}\) found that 8 (14%) of 56 patients with anosmia showed improvement on retesting, although again the type of sensory testing procedure used, if any, was not mentioned and a criterion for improvement was not defined.

The importance of quantitative testing to provide accurate measures of chemosensory function in such studies cannot be overemphasized. The data of our study clearly indicate that many patients are inaccurate in judging the state of their chemosensory functioning. Thus, when asked whether their olfactory function had changed over time, 11 (21.57%) of the patients interviewed reported improved function, whereas only 7 (13.73%) in this group showed empirical evidence of improvement. Of 36 patients who reported no change, 11 (29.95%) actually improved and 10 (26.32%) had regressed significantly. Neither of the 2 individuals who believed their function had declined showed a statistically meaningful decline in UPSIT scores. Such disparities between subjective awareness of olfactory dysfunction and objective test measures have been previously reported\(^\text{29}\) in patients with Parkinson disease. In that study, when asked the question before testing, “Do you suffer from smell or taste problems?” 23 (28%) of 81 patients with Parkinson disease answered the question affirmatively; however, 73 (90.1%) of the 81 patients had UPSIT scores falling below those of their age-, sex-, and race-matched controls.

Parosmia, a condition in which odor quality is altered or in which a strange odor is present in the absence of a stimulus, was common in the study group. Thus, 33% of the patients complained of an ongoing parosmia. This is approximately twice the 16.7% rate reported by Leigh,\(^\text{9}\) nearly 3 times the 13.8% rate reported by Sumner,\(^\text{10}\) and 32% higher than the 25% value reported by Duncan and Seiden.\(^\text{17}\) The higher prevalence of parosmia in our study may reflect such factors as differing definitions of parosmia (or dysosmia), whether the patient was specifically queried about a parosmia problem, and vagaries in sampling. Our finding that the proportion of patients experiencing parosmia decreases as the time since the injury increases suggests that the majority of patients whose parosmia is caused by HT will improve over time. To what degree the decline in frequency of this condition reflects either true disappearance of the parosmic condition or the patient’s ability to ignore (or tune out) this condition requires further study.

In earlier work,\(^\text{3}\) we presented data from a group of patients with smell and taste disorders of heterogeneous origin that suggested depression was greater in those experiencing parosmia or dysgeusia than in those who were not (no distinction was made between parosmia and dysgeusia). In that study, the mean (±SD) BDI score of 362 patients with parosmia was 8.1±7.9, compared with a mean (±SD) of 5.9±6.4 for their nonparosmic counterparts. In the current study, somewhat higher BDI scores were observed across the board; however, no statistically significant difference in BDI scores was found among patients who had never experienced parosmia (mean [±SD] score, 9.1±7.8), those who were experiencing nontransient parosmia (mean [±SD] score, 11.5±8.0), and those who were experiencing transient parosmia (mean [±SD] score, 9.8±7.4). These findings suggest that depression is not meaningfully related to parosmia in HT, and that earlier observations reflect either influences of causes other than HT on BDI scores, the influences of dysgeusia rather than parosmia on such scores, or both. The fact that BDI scores were generally higher in this study than in our previous study suggests that HT may, in fact, be associated with greater depression than that of other conditions (eg, upper respiratory tract infections and nasosinus disease). Alternatively, this could reflect the inclusion of more chronic cases. Recently, in a study\(^\text{26}\) examining depression and dysgeusia, we demonstrated that patients who presented with dysgeusia and comparatively high levels of depression were less likely to recover than patients who presented with dysgeusia and low levels of depression.

It is generally believed that a clear association exists between HT severity and the degree of olfactory dysfunction. For example, Sumner\(^\text{10}\) found that only 44 (4.7%) of 945 patients with HT whose amnesia lasted less than 1 hour exhibited anosmia, compared with 28 (23.7%) of 118 patients whose amnesia lasted more than 1 day. Costanzo and Becker\(^\text{3}\) reported that 43 (19.4%) of 220 patients with moderate head injuries exhibited some form of olfactory disorder, compared with 91 (24.5%) of 372 patients with severe head injuries. Heywood et al\(^\text{27}\) noted an association between scores on the Glasgow Coma Scale and those from an olfactory screening test. Despite such findings, however, anosmia can occur in cases of HT ranging widely in severity and, for this reason, the presence of an association between HT severity and olfactory dysfunction can be masked in some cases. This is a likely explanation for why we found no meaningful statistical association between UPSIT scores and trauma severity (as indexed by duration of unconsciousness or length of...
hospitalization) in our retest group that included patients with anosmia. When patients with anosmia were removed from the sample, such an association was observed. This phenomenon has some precedence in the literature. Sumner\(^1\) reported, “It is clear that the incidence of anosmia increases with increasing severity of the injury, although this rise is not maintained with the most severe injuries.”

Our data are in accord with the notion that occipital blows are more likely to result in anosmia than blows to the front of the head. Of the 128 patients with anosmia for whom the location of HT impact was known, 51 (39.8%) experienced occipital blows and 38 (29.7%) experienced blows to the front of the head. Unique to this study is the observation that blows to the back or side of the head, on average, produce larger deficits in olfactory function than blows to the front of the head (mean [\(\pm SD\)] UPSIT scores: 15.38 [\(\pm 7.96\)], 16.31 [\(\pm 9.99\)], and 19.90 [\(\pm 10.67\)], respectively). However, the occipital-frontal anosmia ratio of this study (4:3) stands in contrast to Sumner’s\(^1\) observation: “In those injuries where there is some anosmia, a blow on the occiput was five times more likely to produce anosmia than a blow on the forehead.”

It is generally assumed that the primary cause of olfactory loss in most head injury cases is the movement of the brain relative to the skull on impact (eg, coup or contre coup movement), resulting in a shearing of the olfactory nerve filaments at the level of the cribriform plate. Frontal impacts cause less olfactory dysfunction than occipital impacts presumably because energy from frontal blows becomes more dissipated (eg, as softer bones or cartilaginous tissues absorb force) than that from blows to the occiput. However, as shown in our MRI studies, considerable damage to temporal and frontal lobe structures is apparent in the majority of head injury cases, making it difficult to rule out the involvement of damage to cortical olfactory structures in severe cases.\(^1\)\(^9\) Yamagishi et al\(^2\) have noted considerable variability in the amount of apparent olfactory tissue remaining in patients with olfactory loss secondary to HT. In their study, biopsy samples obtained from living patients were stained with anti-neuron-specific enolase and S-100 protein antibodies. Despite the fact that in some cases receptor cells and nerve bundles were found to remain, olfactory loss was ubiquitous in this set of patients.

Several previous studies have noted greater olfactory function in patients with parosmia than in patients without parosmia. For example, Duncan and Seiden\(^1\)\(^7\) reported that the mean UPSIT score of 8 patients with HT and parosmia was 20.4, whereas the mean score for 12 patients with HT without parosmia was 12.0. Deems et al\(^3\) noted, in a group of patients with mixed etiology, that the mean UPSIT score of those with parosmia was 19.1, whereas the mean score of those who had never experienced parosmia was 15.9. In the present study, no relationship was found between parosmia and olfactory function when patients with anosmia were included in the evaluation. However, when they were excluded from analysis, olfactory function was found to be lower, not higher, in the patients with HT and parosmia without anosmia. This finding suggests that, in patients with HT with chronic parosmia, the parosmia likely signifies a degenerative process, rather than a regenerative process, possibly within the olfactory epithelium. However, such a link appears not to be strong for long post-HT intervals. Thus, we found that even though the proportion of patients exhibiting parosmia decreased over an 8-year, post-HT interval, there was no evidence of improved olfactory function in such patients over this period.

The present study found decreased olfactory bulb volumes in male, but not female, patients with HT relative to controls. This remarkable sex difference could reflect the more severe HT experienced by males, in accord with the greater degree of HT severity in males that we documented using trauma estimate ratings of nonolfactory bulb structures. However, there is also evidence, albeit circumstantial, that estrogens may protect against olfactory loss from a variety of causes and, thus, could afford some protection from the ultimate loss of olfactory bulb volume. Deems et al\(^3\) reported that only 4 (4%) of 99 postmenopausal women entering the Smell and Taste Center with olfactory loss were taking conjugated estrogens prior to the onset of an olfactory deficit, a percentage significantly lower than the proportion of postmenopausal women in the general population who take such preparations (median, 16%). This finding implies that such preparations may protect against olfactory damage; hence, the reason why a disproportionate number of women not taking such preparations present with olfactory disturbances. Additional work is obviously needed to determine why HT produces a marked decrease in olfactory bulb and tract volumes in men but not women.

A lack of meaningful return of olfactory function in the majority of patients following HT is likely due to, at least in part, incomplete regeneration of the olfactory neuroepithelium and its connections to the olfactory bulb via the foramina of the cribriform plate. Numerous studies suggest that, while the mammalian olfactory neuroepithelium has the propensity for regeneration after cranial nerve I damage, such regeneration is rarely complete. Nevertheless, considerable function may reappear even in the absence of a full complement of cells. For example, hamsters can perform an odor discrimination task with more than 90% accuracy 40 days after bilateral transection of the olfactory receptor axons at the level of the cribriform plate, even though the degree of olfactory system recovery, as measured by the amplitude of evoked potentials within central neural structures, is markedly reduced even 120 days after the transection.\(^29\)\(^30\) An analogous return of olfactory function following exposure of rats to airborne toxicants has been noted despite an absence of full recovery of the epithelium from toxin-induced damage.\(^31\)\(^32\) Indeed, the preexposure complement of receptor cells is never fully attained and major sectors of the olfactory epithelium become disorganized and replaced by respiratory-like epithelium.\(^33\) Biopsy specimens of human olfactory neuroepithelium from patients with HT suggest similar changes. Thus, the number of ciliated olfactory receptor cells seems to be greatly reduced and, of the few dendrites that reach the surface,
only a minority exhibit cilia. The layered appearance seen in normal epithelia typically disappears, and cranial nerve I axon fascicles often seem displaced within the epithelium and lamina propria, which is punctuated with many metabolically active and pyknotic neurons.34-36 These observations imply that some new receptor cells develop following the trauma-induced axotomy and sprout axons, but the axons are unable to penetrate the fibrosis around the cribiform plate.

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