
Philippe Rombaux, Caroline Huart, Naima Deggouj, Thierry Duprez and Thomas Hummel

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What is This?

Philippe Rombaux, MD, PhD¹, Caroline Huart, MD¹, Naima Deggouj, MD¹, Thierry Duprez, MD², and Thomas Hummel, MD, PhD³

Abstract

Objectives. Several prognostic factors influencing the recovery from olfactory dysfunction have been described. The aim of this study was to investigate whether olfactory bulb volume could be used as a new predictor of olfactory recovery in postinfectious and posttraumatic olfactory loss.

Study Design. Cohort study; Level of evidence, 4.

Setting. Tertiary university clinic, department of otolaryngology.

Subjects and Methods. A cohort of 60 patients with postinfectious (n = 28) and posttraumatic olfactory loss (n = 32) was investigated. Assessment of olfactory function was performed using orthonasal (Sniffin’ Sticks test) and retronasal psychophysical olfactory tests, at the time of the diagnosis (t1) and 15 months later (t2). All patients were examined on 3 tesla magnetic resonance imaging, and the olfactory bulbs volume was assessed using planimetric contouring at the time of the diagnosis (t1).

Results. Recovery rate was 25% in patients with posttraumatic olfactory loss and 36% in patients with postinfectious olfactory loss. There was a correlation between both orthonasal and retronasal olfactory testing and the initial measurement of the total olfactory bulb volume. In addition, we observed a significant correlation between changes in olfactory functions and initial measurement of the total olfactory bulb volume, with larger volumes relating to higher improvement of olfactory function. Finally, we found that none of the patients with a total olfactory bulb volume of 40 mm³ or less exhibited recovery of olfactory function.

Conclusion. Olfactory bulb volume seems to be a predictor of olfactory recovery in patients with postinfectious and posttraumatic olfactory loss.

Keywords

olfaction, olfactory bulb, MRI

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Olfactory dysfunction is extremely common (affecting up to 20% of the general population), and several studies have shown that olfactory disorders have a negative impact on quality of life and may predispose affected people to severe alterations of food intake and behavior.

In “smell clinic” centers, etiologies of olfactory disorders are encountered as follows: postinfectious, posttraumatic, sinonasal related (ie, chronic rhinosinusitis), congenital, neurologic, toxic, or idiopathic olfactory loss. In sinonasal-related olfactory dysfunction, which accounts for 14% to 30% of cases of olfactory dysfunction, medical and surgical therapies may lead to an improvement in or even recovery of olfactory function. Although the field of olfaction has had considerable development in the past year, therapies leading to recovery are still missing in postinfectious and posttraumatic olfactory loss. Because many patients with olfactory dysfunction cannot benefit from a treatment, a precise clinical workup procedure is mandatory to accurately assess their olfactory deficit and, hence, to provide them appropriate counseling. Therefore, patients with olfactory disorders undergo several clinical examinations such as psychophysical olfactory testing (orthonasal and retronasal), imagery of the chemosensory pathways using magnetic resonance imaging (MRI), and electrophysiological

¹Université Catholique de Louvain, Institute of Neurosciences, Unit of Otorhinolaryngology, Cliniques Universitaires St Luc, Brussels, Belgium
²Université Catholique de Louvain, Institute of Neurosciences, Unit of Medical Imaging, Cliniques Universitaires St Luc, Brussels, Belgium
³Unit of Otorhinolaryngology, University of Dresden Medical School, Dresden, Germany

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Corresponding Author:
Philippe Rombaux, MD, PhD, University of Louvain, Unit of Otorhinolaryngology, Cliniques Universitaires Saint Luc, Av. Hippocrate 10, 1200 Brussels, Belgium
Email: philippe.rombaux@uclouvain.be
evaluation with recording the so-called chemosensory event-related potentials. Altogether, the results of this complete clinical evaluation allow the clinician to draw a prognosis of recovery. The clinician can then provide the most complete and clear information to the patient, helping him or her to manage sensory deficit, adopt coping strategies, and be informed about the future expectations he or she may have.

We know from previous publications that prognosis is influenced by sex, age, severity of the sensory deficit (based on the psychophysical test results), the origin of the olfactory disorder, the presence of qualitative olfactory dysfunction,11,12 and the recording of olfactory event-related potentials at the time of diagnosis.13 In addition, it is well known that the olfactory bulb (OB) plays a central role in olfactory perception, and it has been established that the OB volume assessed by manual planimetric contouring on MRI is correlated with olfactory function.14-18 We might thus hypothesize that OB volume could also be used as a predictor of olfactory recovery.

The aim of this study was to evaluate whether the OB volume measured at the time of diagnosis may be a prognostic value for the recovery of patients with olfactory loss secondary to a trauma or an upper respiratory tract infection. In this cohort of patients, recovery of olfactory function was diagnosed based on the psychophysical evaluation of olfactory function.

Materials and Methods

Subjects

This study was carried out in 60 patients (32 patients with a posttraumatic olfactory loss and 28 with a postinfectious olfactory loss). All patients provided written informed consent before entering the study.

Diagnosis of postinfectious olfactory loss was made when patients claimed that the olfactory deprivation started after an upper respiratory infection and lasted until the consultation, in the absence of other causes of olfactory loss. Diagnosis of posttraumatic olfactory loss was made when a cranial trauma was present in the patient’s history and when no other cause of olfactory loss was observed. Delay between upper respiratory tract infection or cranial trauma and the time of diagnosis was reported. Patients were examined at 2 different occasions: at the time of diagnosis (t1) and approximately 15 months later (t2). Olfactory function was assessed psychophysically at t1 and t2, whereas MRI was only performed at t1. None of the patients received any medical therapy or were asked to perform olfactory training. The criterion for improvement was an increase of more than 5 points in the TDI (threshold, discrimination, and identification) score.19 Investigations were approved by the “Commission d’Ethique Biomédicale Hospitalo-Facultaire de l’Université catholique de Louvain” (Belgium).

Psychophysical Testing

Orthonasal olfactory function. Olfactory function was assessed orthonasally using the validated Sniffin’ Sticks test.20,21 In this test, odors are presented to the subjects using felt-tip pens placed approximately 2 cm in front of both nostrils, as follows. First, the “olfactory threshold” (T) is assessed using n-butanol presented by means of a single stair-case, using stepwise dilutions in a row of 16 felt-tip pens. Second, “odor discrimination” (D) is assessed by asking subjects to perform a 3-alternative forced-choice task using 16 pairs of odorant. Third, “odor identification” (I) is assessed by asking subjects to identify 16 individual odors by performing a forced choice from a list of 4 verbal descriptors. Scores from olfactory threshold (T), discrimination (D), and identification (I) were then added up to provide the TDI score,20,21 out of 48. Normosmia is defined as a TDI score >31. Hyposmia is defined as a TDI score ranging between 16 and 31, and anosmia is defined as a TDI score <16.22

Retronasal olfactory function. Retronasal olfactory performances were evaluated following a standardized method using a row of 20 items. Powderized substances were applied in the middle of the tongue inside the oral cavity using squeezable plastic vials. Each substance was identified by means of a forced-choice procedure between 4 proposals.23

OB Volume

Subjects were examined following a standard protocol on a 3 tesla MRI system (Achieva, Philips Healthcare, Best, the Netherlands) with an 8-channel phased-array head coil. A T2-weighted fast spin-echo sequence specifically dedicated to the analysis of the OB was performed with the following parameters: repetition time (TR) = 2066 ms, echo time (TE) = 80 ms, echo train length = 13, slice thickness = 2 mm with no gap, field of view = 160 × 130, acquisition matrix = 340 × 273 (in-plane resolution = 0.47 × 0.48 mm²) and reconstruction matrix = 512 × 512 (in-plane resolution = 0.31 × 0.31 mm²), number of signal average = 4, and acquisition time = 5 min, 51 s.

The 23 slices were placed in a coronal plane perpendicular to the cribriform plane and covered the middle segment of the basifrontal area. The OB volume was calculated by planimetric manual contouring on each slice where it was present in the coronal plane, and surfaces were multiplied by the 2-mm thickness of slices to obtain a volume in cubic millimeters.24 Measurements were performed twice by 2 observers. When the volumes showed a difference of more than 10%, a third observer performed a third measurement. A mean of these measurements was calculated and included into the database as the definitive volume to be used for statistical analyses.

The normal OB volume for people <45 years old should be more than 58 mm³, and the normal OB volume for people >45 years old should be more than 46 mm³.18

Statistical Analysis

Statistical analyses were performed using the Medcalc Software Release 9.1 (MedCalc Software, Mariakerke, Belgium). The significance level was set at P < .05. Psychophysical scores and OB volumetric measurement values were submitted to the t test for independent samples. Pearson’s correlation coefficients between volumetric
measurements of the OB and psychophysical scores were calculated.

**Results**

The mean age of the 60 patients was 50.0 years (range, 24-79 years), with 21 men and 39 women.

The mean age of patients with postinfectious olfactory loss was 59.7 years (range, 27-79 years), with 9 men and 19 women. The mean duration time between the olfactory loss and the time of diagnosis was 15.9 months. The mean TDI score at the time of the diagnosis was 16.7, ranging from 7 to 26. In the posttraumatic olfactory disorder group, the mean age was 41.6 years (range, 24-74 years), with 12 men and 20 women. The mean duration time between the olfactory loss and the time of diagnosis was 14.8 months. The mean TDI score at the time of the diagnosis was 13.0, ranging from 5 to 28 (Table 1).

Thirty-six percent (10 of 28) of the patients with postinfectious olfactory dysfunction and 25% (8 of 32) of the patients with posttraumatic olfactory loss showed an improvement in their olfactory function at the second examination. At the level of the entire cohort, the percentage of patients showing an improvement was 30% (18 of 60). Mean time between the onset of olfactory loss and time of diagnosis was 16.4 months, and the mean time between the 2 evaluations at t1 and t2 was 14.6 months (Table 1).

**Correlation between TDI Score and Olfactory Bulb Volume**

At the whole group level, there was a correlation between the TDI score and the initial total (right + left) OB volume at t1 ($r_{60} = 0.40$ and $P = .0016$). Retronasal olfactory function at t1 also correlated with the initial total OB volume ($r_{60} = 0.46$, $P = .0021$).

Patients were divided in 2 groups: (1) patients showing an improvement in olfactory function and (2) patients who did not improve. When comparing the 2 groups, there was no difference regarding the initial olfactory scores (odor thresholds, discrimination, and identification, TDI score: $P > .25$) or the interval between the onset of the olfactory disorder and first measurement of olfactory function ($P = .19$). However, when comparing the 2 groups with regard to olfactory function, patients with initially larger OB volumes exhibited significantly better olfactory function at the second session (improvement group: total OB volume = 85.26 ± 21.64; no-improvement group: total OB volume = 46.18 ± 20; $P < .001$).

Most important, significant correlations were observed between changes in olfactory function and the initial measurement of the total OB volume, with larger volumes relating to higher improvement in olfactory function (thresholds: $r_{60} = 0.26$, $P = .043$; discrimination: $r_{60} = 0.42$, $P = .001$; identification: $r_{60} = 0.45$, $P < .001$; TDI score: $r_{60} = 0.54$, $P < .001$) (Figure 1). This was also true when considering each subgroup separately (postinfectious TDI score: $r_{28} = 0.50$, $P = .007$; posttraumatic TDI score: $r_{22} = 0.65$, $P = .0001$) but also when considering separately patients older and younger than 60 years (patients <60 years old: $r_{38} = 0.55$, $P < .0001$; patients >60 years old: $r_{22} = 0.53$, $P = .012$).

Finally, on a descriptive level, we found that none of the patients with a total OB volume of 40 mm$^3$ or less exhibited recovery of olfactory function (Figure 2).

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**Table 1. Descriptive Characteristics of the 60 Patients Indicating the Mean Values for Age, t0-t1 Duration, t1-t2 Duration, TDI Score at t1 and t2, and Total OB Volume**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Age, y</th>
<th>t0-t1, mo</th>
<th>t1-t2, mo</th>
<th>TDI Score (t1)</th>
<th>TDI Score (t2)</th>
<th>Total OB Volume (t1), mm$^3$</th>
<th>Improvement, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>60</td>
<td>f = 39, m = 21</td>
<td>50</td>
<td>16.4</td>
<td>14.6</td>
<td>14.7 (13.3-16.4)</td>
<td>18.8 (17.4-20.5)</td>
<td>58.36 (51.2-65.46) [14-119]</td>
</tr>
<tr>
<td>Postinfectious</td>
<td>28</td>
<td>f = 19, m = 9</td>
<td>59.7</td>
<td>15.9</td>
<td>14.4</td>
<td>16.7 (14.6-18.8)</td>
<td>20.6 (17.8-23.4)</td>
<td>67.56 (58.34-76.77) [34-119]</td>
</tr>
<tr>
<td>Posttraumatic</td>
<td>32</td>
<td>f = 20, m = 12</td>
<td>41.6</td>
<td>16.8</td>
<td>14.8</td>
<td>13.0 (11.2-14.7)</td>
<td>17.3 (15.2-19.3)</td>
<td>50.30 (40.06-60.55) [14-110]</td>
</tr>
</tbody>
</table>

The 95% confidence interval for the TDI (threshold, discrimination, and identification) score and total olfactory bulb (OB) volume and improvement are indicated in parentheses. The range for the total OB volume is indicated in brackets. Abbreviations: f, female; m, male; t0-t1, time between the olfactory loss and the diagnosis in months; t1-t2, time between the 2 clinical evaluations in months.
hyposmia vs anosmia). Age and sex also seem to be important in the assessment of the prognosis since women and younger patients tend to recover more frequently than do men and older patients. Another possible prognostic factor is the duration of the disease, although results are more controversial for this factor. Electrophysiological measures are also predictive of recovery since it was demonstrated that the presence of olfactory event-related potentials at the time of diagnosis is linked to a better outcome in patients with postinfectious olfactory loss. With regard to the meaning of qualitative olfactory disorders such as parosmia and phantosmia, reports have been mixed in relation to the likelihood of recovery.

In this study, we did not find any difference regarding the initial olfactory function between the group that improved and the group that did not. This might be explained by larger cohorts of patients investigated in previous studies. In addition, the duration of the disease was not different in both groups. This is in line with a previous study by Hummel and Lotsch, who showed that the improvement in olfactory function was not significantly related to the duration of the disease.

In this study, we have chosen to study exclusively MRI scanning in postinfectious and posttraumatic cases because they represent the larger subgroup of patients in our smell clinic center and also because they seemed to be unrelated to other confounding factors such as medications, previous surgery, or neurological disorders.

As indicated in previous studies, we have noted that the capacity for regeneration is higher in patients with postinfectious olfactory loss as compared with patients with posttraumatic olfactory loss. This is assumed to be due to the fact that neural connections are impaired but not destroyed in postinfectious olfactory loss, whereas neural connections are lost in many cases of posttraumatic olfactory loss. This hypothesis is reinforced by literature reporting that the prognosis seems to be better in the postinfectious group than in the posttraumatic group.

It has been established that the OB volume is correlated with olfactory function in normal subjects as well as in different clinical entities. Buschhüter et al showed that individual variation in OB volume was large in the normal population and that the OB volumes are relatively stable up to the fourth decade of life and declined in the sixth and seventh decades. In addition, the olfactory bulb shows a high degree of plasticity, as demonstrated in early blind subjects or in patients with sinonasal-related olfactory dysfunction after endoscopic sinus surgery. Results of the latter study confirmed that OB volume is well correlated with orthonasal or retronasal scores, even in patients with an olfactory disorder. Nevertheless, the role of the OB volume as a prognostic tool remained hypothetical and was investigated here. In our study, we confirm that the prognosis may be based on the OB volume in both postinfectious and posttraumatic diseases, with larger volumes relating to higher improvement on a population level. Nevertheless, it is difficult to predict the individual benefice
of a large olfactory bulb. On the other hand, the cutoff value of 40 mm³ total OB volume seems to be important to mention. Indeed, in our population of patients, none of the patients with a total olfactory bulb volume of less than 40 mm³ improved. This value has thus a sensitivity of 100% and might be a useful indicator at an individual level. This merits further investigations in a larger population.

Until now, no medical treatment has shown a beneficial effect on recovery in humans with a postinfectious or a postraumatic olfactory dysfunction. Because olfactory dysfunction severely impairs the quality of life and the daily life (cooking, detection of potentially dangerous odors) of patients²,³,32 and is associated with a higher prevalence of mild to severe depression as compared with the general population,³³ the affected patient should be offered a complete evaluation to formulate a prognosis of recovery. Finally, a recent study indicates that olfactory training leads to an improvement in olfactory function. We should thus propose this treatment to patients and encourage them to perform this training twice a day.²⁴

To conclude, we have shown that the initial measurement of the OB volume is significant for olfactory prognosis at the group level, and hence we propose that it should be further considered in the assessment of patients with postraumatic or postinfectious olfactory loss. An MRI examination is thus useful in the clinical workup procedure of such patients. Although OB volume has received close attention for the diagnosis of olfactory disorder, we have demonstrated that it should receive further considerations for the prognosis of recovery.

Author Contributions
Philipp Rombaux, concept and design of the study, acquisition of data, analysis and interpretation of data, drafting and writing the original manuscript, reviewing the manuscript and approving the latest version; Caroline Huart, acquisition of data, analysis and interpretation of data, writing the original manuscript, reviewing and approving the latest version; Naima Deggouj, analysis and interpretation of the data, critically revising the manuscript and approving the latest version; Thierry Duprez, acquisition of the data, analysis and interpretation of data, drafting and writing a section of the original manuscript, approving the latest version; Thomas Hummel, analysis and interpretation of the data, critically revising the manuscript and approving the latest version.

Disclosures
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