Olfactory Bulb and Tract and Temporal Lobe Volumes

Normative Data across Decades

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ABSTRACT: The sense of smell shows a diminution with age as measured by the University of Pennsylvania Smell Identification Test (UPSIT). To ascertain whether the volumes of the olfactory bulbs and tracts (OBTs) and the temporal lobes (TL) declined in parallel to smell function, we examined 36 individuals from ages 22 to 78 who did not complain of any loss of the sense of smell using magnetic resonance (MR) imaging. The OBT volumes showed an initial increase to the 4th decade of life and then a decrease with increasing age, while the trend in TL volume was not as dramatic. There was no correlation between OBT or TL volumes with unilateral or total UPSIT scores. The normative data by decades can be used to assess the OBTs of cohorts of patients with neurodegenerative disorders that affect olfaction.

INTRODUCTION

Odorants enter the nose and stimulate neuroepithelial receptor cells located along the roof of the nasal cavity. The axons of these olfactory receptor cells coalesce into bundles which pass through the cribriform plate to synapse with glomeruli of the olfactory bulb. The second order neurons of the olfactory bulbs pass through the olfactory tracts to enter the brain via the medial and lateral olfactory striae. The connections to central locations in the brain are numerous and widely spaced, but include the piriform cortex, the entorhinal cortex, the orbitofrontal cortex, the anterior olfactory nucleus, the periamygdaloid-hippocampal region, and the hypothalamus. There are numerous other tertiary connections to the limbic and autonomic systems in the brain.

The number of glomeruli in the olfactory bulb are said to decrease with age in humans. This would suggest that the volume of the olfactory bulbs and tracts (OBTs) might decrease with advancing age; however, this has not been demonstrated in vivo to date. The size of the OBTs has been previously studied in patients with congenital anosmia, posttraumatic chemosensory deficits, and neurodegenerative disorders. However, these studies lacked normal control group data for OBT volumes across the various age ranges studied. We sought to provide such data using magnetic resonance (MR) imaging volumetric analysis.

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MATERIALS AND METHODS

Thirty-six individuals, 17 women and 19 men, who reported a normal sense of smell were referred for smell testing and volumetric MR scanning at the University of Pennsylvania Medical Center. The patients had extensive review of their clinical histories in order to exclude a possible cause of smell dysfunction. The subjects were divided into decades of age (see Table 1), and there were at least 5 subjects per decade studied. All patients signed approved Institutional Review Board (IRB) consent forms for participation in this study.

The patients underwent the 40-item University of Pennsylvania Smell Identification Test (UPSIT) (20 items to each side). We used this smell test to evaluate for any unexpected chemosensory deficits. The UPSIT is one of the most widely used tests of odor identification in the world and is a standard for determining whether a patient can identify smells.1 The smell testing was scheduled within the same week as the MR scan.

MR scans of the OBs employed a 5-inch round general purpose receive only surface coil placed over the nasion. After a sagittal localizing scan, coronal images with parameters of 500/15/2 (repetition time/echo time/number of averages) were performed with 3-mm interleaved scans and a 256 × 256 matrix with a 12-cm field of view. Using this protocol and a surface coil one can clearly and reproducibly identify the olfactory bulbs and tracts and trace them posteriorly (Fig. 1a–c).

The examination of the TLs consisted of a sagittal localizing scan followed by coronal T1-weighted scans (600/11/1) with 3-mm contiguous sections, a 25-cm field of view, and a 256 × 256 matrix. These scans were performed through the TLs using the standard bird-cage design head coil (Fig. 1d). The data from the OBT and TL coronal scans were transferred to an ISG Technologies Allegro workstation for volumetric analysis.

Volumes were determined for the right and left OBTs and TLs by two independent evaluators based on tracing, thresholding, and three-dimensional (3-D) volumetric processing. The olfactory bulb was identified at the anterior cribriform plate, and the olfactory tract was followed posteriorly to its entrance to the brain and septal nuclei below the rostrum of the corpus callosum—both the bulb and tract were included in the OBT volumes. In order to assess interobserver reliability, intraclass correlation coefficients were performed for pairs of readings between readers for right and left olfactory bulb-tract volumes. The percentage interobserver difference between the two observers' OBT volume measurements was also computed.

Intraclass correlation coefficients (ICC) and percentage interobserver variations have been previously published for intraobserver OBT volumes and inter- and intraobserver reliability for temporal lobe volumes.2 In that study, the ICCs ranged from 0.919 to 0.925 for intraobserver OBT variation, 0.950 for intraobserver TL variation, 0.945 for interobserver OBT variation, and 0.923 for interobserver TL variation.

### Table 1. Composition of Study Group

<table>
<thead>
<tr>
<th>Decade</th>
<th>Men</th>
<th>Women</th>
<th>Mean Age (Years)</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>3rd</td>
<td>2</td>
<td>3</td>
<td>24.8</td>
<td>2.4</td>
</tr>
<tr>
<td>4th</td>
<td>4</td>
<td>3</td>
<td>32.8</td>
<td>3.3</td>
</tr>
<tr>
<td>5th</td>
<td>3</td>
<td>3</td>
<td>42.7</td>
<td>3.3</td>
</tr>
<tr>
<td>6th</td>
<td>3</td>
<td>3</td>
<td>55.0</td>
<td>2.4</td>
</tr>
<tr>
<td>7th</td>
<td>3</td>
<td>3</td>
<td>65.2</td>
<td>3.2</td>
</tr>
<tr>
<td>8th</td>
<td>2</td>
<td>4</td>
<td>74.0</td>
<td>2.4</td>
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<tr>
<td>Totals</td>
<td>17</td>
<td>19</td>
<td>49.6</td>
<td>17.4</td>
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FIGURE 1. OBT and TL. (a) This coronal T1-weighted MR image demonstrates the normal appearance of the anterior-most portions of the right and left olfactory bulbs (arrows) with dark cerebrospinal fluid above and the nasoethmoidal region below. (b) Further posteriorly, one can see the olfactory tracts (arrows) under the cerebrospinal fluid filled olfactory sulci (arrowheads). (c) The tracts (arrows) tend to get smaller and smaller as they course posteriorly to enter the brain. The optic nerves (o) at the level of the orbital apex are well seen on this scan. (d) The temporal lobe (T) volume was measured from head coil coronal T1-weighted MR images. The borders used were the Sylvian fissure (arrowheads) superiorly and posteriorly, the hippocampus (curved arrows) medially and the skull borders laterally, anteriorly, and inferiorly.
and 0.924 for interobserver variation on TL values. The percent variation between observers for TL volumes was 3.1–4.2% and was 11.3–14.6% for OBTs. Phantom studies reported in the same study showed MR volumetric accuracy rates within 5.0–6.2% of true volumes measured by water displacement techniques. Because of the near perfect ICCs and the low percent variation in multiple readings of TL volumes, one observer measured the TL volume.

RESULTS

The UPSIT scores for each decade are noted in Table 2. The mean UPSIT scores for the individuals in the third decade (the youngest group studied) were the highest, while the mean score for those in the 7th and 8th decades was the lowest, but there were no significant differences in the scores between groups. Some individuals did not score within the expected norms for age. One woman aged 72 had an UPSIT score of 31, one 69-year-old man had an UPSIT score of 28, one 64-year-old man had an UPSIT score of 30, one 64-year-old woman had an UPSIT score of 32, one 44-year-old man had an UPSIT score of 31, and one 40-year-old man had an UPSIT score of 32. All of the other subjects had UPSIT scores ≥ 33.

The left and right OBT volumes peaked in the 4th decade at 158.7 and 145.5 mm³, respectively, but showed considerable variation within each subject group (see Table 3, Fig. 2). The mean OBT volumes for each side and the mean of both sides showed a decline in the 7th and 8th decade that paralleled the decline in UPSIT scores. A Kruskal-Wallis test, performed to detect differences between the means of OBT volumes between decades showed borderline significance at p = 0.05 for the left OBT, but not the right. The biggest differences noted were between the 4th and 7th decade for right and left OBTs.

By treating the left and right OBT measurements for each person as multiple mea-
measurements of a single quantity (OBT volume for that person) one can increase the ability to detect differences across decades. However, these two measurements for each person are correlated which poses statistical problems for 'independent samples.' A recent methodology for the analysis of repeated measurements, generalized estimating equations (GEE), allows for regression models to be fit taking the correlation between the two OBT volumes for each person into consideration. Using regression based on the GEE model we find that OBT volumes do show significant decreases between decades ($p = 0.027$).

The temporal lobe volumes showed marked variation with age as evidenced by the wide standard deviations (see Table 4, Fig. 3). No definite trends in the volumetric measurements were identified and the Kruskal-Wallis test did not detect differences across decades.

**TABLE 4. Temporal Lobe Volume vs Decade of Life**

<table>
<thead>
<tr>
<th>Decade</th>
<th>Mean Left TL Volume (mm$^3$)</th>
<th>Standard Deviation</th>
<th>Mean Right TL Volume (mm$^3$)</th>
<th>Standard Deviation</th>
<th>Mean TL Volume (mm$^3$)</th>
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</thead>
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<tr>
<td>3rd</td>
<td>75737</td>
<td>6378</td>
<td>76561</td>
<td>2134</td>
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<tr>
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<tr>
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<td>70334</td>
<td>10024</td>
<td>73142</td>
<td>9877</td>
<td>71738</td>
</tr>
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</table>
FIGURE 3. Left and right temporal volumes by decade.

We performed a Spearman rank correlation coefficient and did not find any relationship between OBT volumes and UPSIT scores or TL volumes and UPSIT scores.

The ICCs for the 2 readers were 0.92 for the right OBT volume and 0.94 for the left OBT volume, indicating outstanding agreement. The mean difference between the two observers for the 72 pairs of OBT measurements was 6.8% (range 1.0–17.4%).

DISCUSSION

As measured by total UPSIT scores, there is an initial increase in odor identification capability to the third decade of life, at which time the UPSIT scores plateau. At about age 60, however, a decline in median UPSIT scores begins to be seen across subjects to the point that nearly 75% of individuals over 80 years old score 19 or less on the 40-item UPSIT test (see Fig. 4). Similar changes in odor threshold values for phenylethyl alcohol are noted; however, the drop-off starts to be seen at about age 40 in men and 60 in women. Smokers and men tend to have higher thresholds than nonsmokers and women, respectively. A change in the perception of pleasantness of taste also occurs with age. This effect can be eliminated when the nostrils are occluded and the olfactory influence on taste is nullified. Some believe that the sense of smell declines with age due to 1) a reduced volume of the sensory neuroepithelium due to cumulative effects of viral infections, 2) replacement of the olfactory neuroepithelium with nonsensory columnar epithelium in the olfactory clefts of the nose, 3) diminution in central neurotransmitters (e.g., nor-
Females (n = 1158)
Males (n = 797)
Total group (n = 1955)

FIGURE 4. Median UPSIT scores vs age, showing decline in olfaction after age 60. (From Doty et al. Reprinted by permission from Science.)

epinephrine), 4) reduced patency of the airway, 5) variations in the nasal cycle with age, or 6) reduced resistance of the olfactory neuroepithelium to infectious or toxic insults. Smith noted a diminution in the receptor elements of the olfactory neuroepithelium that was more apparent after the 5th decade of life. In rats, the actual volume of the olfactory bulb components decreases after 2 years of age. These rat findings have not been duplicated in living human olfactory bulbs and tracts until this report.

We believe that the finding of a decline in the human OBT volume with advancing age lends credence to the idea of a reduced amount of afferent input to the olfactory bulbs and tracts from the olfactory neuroepithelium and ciliated nerves that pierce the cribriform plate. A decrease in central neurotransmitters is a less plausible explanation for our quantitative findings, since the predominant effect seen is at the bulb and tract level, not at the cortical level.

There is a large variation in OBT volumes even within subjects in the same decade of life, reflected in the wide standard deviations reported herein. Part of these differences may reflect the effects of gender, height, head circumference, and body habitus. The small sample size within each grouping of age precludes adequate analysis of these potential covariates. The broad standard deviations also suggest that looking at a single individual's OBT volume may not be as useful as studying large cohorts of subjects to detect a statistically significant difference in OBT volume from normals.

Having healthy control standards for OBT volumes for different decades of life would be helpful for evaluating pathologic conditions which are associated with olfac-
tory loss. What groups may be best evaluated with a volumetric technique? We have previously shown absence or hypoplasia of OBTs in patients with congenital anosmia and marked volume loss in subjects with posttraumatic olfactory deficits. The neurodegenerative disorders that affect olfaction, including Parkinson’s disease, Huntington’s disease, and non-Alzheimer’s dementia are also amenable to evaluation by MR volumetric techniques. As an example, patients with Alzheimer’s disease have incredibly abundant neurofibrillary tangles and neuritic plaques in their OBTs and smell loss early in their course. Will OBT volume reflect extent of disease and/or degree of chemosensory deficit?

While we believe that volumetric studies offer the best means of evaluating the morphology of the OBTs, functional magnetic resonance imaging (fMRI) shows promise in providing knowledge of how the cortical regions of the brain process odors. The ability to evaluate the OBTs via fMRI is severely limited due to their small size and location at the base of the brain. The susceptibility artifacts in this region during an fMRI experiment and slice thickness limitations preclude adequate visualization of the OBTs. However, the central connections to the frontal lobes and temporal lobes can be visualized with fMRI in a reliable and reproducible fashion, given paradigms that effectively expose the nose to odors in a rapid on-off fashion. A combined approach of morphologic volumetric studies and physiologic fMRI scans may provide the best means for fully evaluating patients with chemosensory deficits.

REFERENCES