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## **Evaluation of olfactory bulb volume and olfactory sulcus depth development with 3 Tesla MRI in childhood**

B. Güney et al., Pediatric olfactor development between 1 month and 17 years

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### **ABSTRACT**

**Background:** In this study, it is aimed to reveal the change in OBV and OSD in healthy Turkish pediatric individuals between 1 month and 18 years of age with 3 Tesla MRI taking into account different age groups and gender factors.

**Materials and methods:** In this retrospective study, 190 pediatric individuals who underwent cranial MRI were evaluated. Healthy pediatric cases were divided into four groups as infantile period (first 24 months when cerebral myelinization was completed), early childhood (2-6 years), childhood (6-12 years) and adolescence (12-18 years). OBV and OSD measurements were performed on coronal T2-weighted brain MR images by 3T MR scan. The mean, right and left olfactory bulb volume and sulcus depths were used for evaluation.

**Results:** The mean age was  $9.9 \pm 7.5$  months for the infantile period,  $4.5 \pm 1.3$  years for early childhood,  $9.3 \pm 1.7$  years for childhood and  $15.2 \pm 1.7$  years for adolescence. Mean, right and left OBV was found to be slightly larger in male children than female children ( $P= 0.015$ ,  $P= 0.033$  and  $P= 0.010$ , respectively). There was no statistical difference between the genders for mean, right and left OSD ( $P= 0.559$ ,  $P= 0.536$  and  $P= 0.598$ , respectively). Among the age groups, the values of the 3rd and 4th groups in terms of mean, right and left OBV were higher than the other two groups ( $P<0.001$ ). In terms of OSD, mean, right and left values were higher in group 2, 3 and 4 than group one ( $P<0.001$ ).

**Conclusions:** These data differ by pediatric age group and gender for the development of OBV and OSD. Normal values for the pediatric age group and gender should be calculated to detect olfactory dysfunction.

**Key words:** pediatric age, bulbus olfactorius, olfactory sulci, 3 Tesla MR

## **INTRODUCTION**

The sense of smell is one of the five senses that have an important function in human life, and the olfactory bulb (OB) is considered to be the most important transmission station in processing the sense of smell. Anatomical structures of the sense of smell begin to develop early in the human fetus. There are studies and anatomical atlases on the development and anatomical change of the primordial olfactory bulb, which was first observed anatomically in a 41-day (4.5 week) embryo in the fetal development period, from gestation to birth [2, 13, 15,17]. However, the number of studies on the anatomical development and change of the olfactory bulb in the pediatric period is limited. In a study conducted by Schneider et al about the maturation of the olfactory bulb in the postnatal period, they found that olfactory bulb showed a similar maturation parallel to the maturation of the cerebral white matter until the end of the second year, when the myelination and maturation of the cerebral white matter was completed. In this study, it was found that the olfactory bulbs took the adult shape at the end of the postnatal 24 months [18]. The first study on the anatomical development and change of olfactory bulb volume in the pediatric age group was conducted by Hummel et al [10]. A positive relationship was found between increased OBV and increased olfactory function in this study performed in children aged 1 to 17 years. It was found that both OBV and olfactory function increased with age.

Another parameter used in evaluating olfactory functions is the depth of the olfactory sulcus. Some diseases such as major depression, anxiety disorder, Behçet's disease, Parkinson's and Alzheimer's disease have been shown to reduce the depth of the olfactory sulcus and cause a decrease in the sense of smell [1, 5, 11]. There are limited studies on the change of olfactory bulb volume and olfactory sulcus depth with age in pediatric cases [16]. OBV and OSD are known to vary with age (4, 10). The age-related change and normal values of both OB and OSD in healthy pediatric individuals are not clearly known.

In this study, it is aimed to reveal the change of OBV and OSD over time in healthy Turkish pediatric individuals between 1 month and 18 years of age with 3 Tesla MRI taking into account different age groups and gender factors.

## **MATERIALS AND METHODS**

After being approved by the ethics committee of our university, the research was started retrospectively in the Radiology department. Only children with normal brain MRI

were included in the study. Pediatric individuals with any brain abnormality (developmental anomaly, myelinization disorder, maturation disorder, etc.) or disease were excluded from the study. While evaluating the patients, the patient files registered in the hospital information system were taken as basis. Those with a genetic disease in their family, those with suspected congenital neurometabolic disease, chronic diseases such as diabetes mellitus and hypertension, and asthma patients were excluded from the study. Patients who had MRI examination for control purposes and patients with nonspecific symptoms and no pathology were included in the study. The cases had nonspecific complaints such as headache and dizziness in order of frequency. No disease was detected in these pediatric individuals and no disease developed during clinical follow-up in our hospital.

In this study, 190 pediatric individuals who underwent cranial MRI between 2017-2019 were evaluated retrospectively. Cases with good image resolution and no motion artifact were included in the study, while cases with poor image resolution and artifacts were excluded. 95 of our cases were women and 95 were men. Healthy pediatric cases were divided into four groups according to their age and gender: group 1: infantile period (1-24 months), group 2: early childhood (2-6 years), group 3: childhood (7-12 years) and group 4: adolescence (13-18 years); group A consisting of 95 women; group B consisting of 95 men. The study was conducted on the basis of and in accordance with the declaration of Helsinki. OBV and OSD measurements were made on T2-weighted brain MR images in the coronal plane (figure 1) obtained on a 3 Tesla MR (Magnetom Skyra, Siemens, Germany) device. Our imaging parameters were 256x256 matrix and 22 cm field of view (FOV), repetition time = 3500 ms (TR 3500 ms), echo time = 75 ms (TE 75 ms), excitation number = 2 (NEX 2), and a slice thickness of 4 mm. OBV and OSD measurements were made by two experienced radiologists who had no knowledge of the cases.

Volumetric measurement of OBV was made using 3D Slicer software (3D Slicer software ver. 4.2.2-1, <http://www.slicer.org>). The Slicer volumetric measurement program is a free open source software package developed by Harvard University and approved for medical research. After dividing the olfactory bulb into sections with appropriate threshold values in the coronal image, separate MR numbers were assigned to each image with the Slicer software. ROI (region of interest) was adjusted to not exceed the anatomical contours of the bulb. After each slice containing the relevant OB sections was revealed, a three-dimensional graphical model of the OB was created and volume calculation was made. Intra-observer variability was set at less than 5%.

## **Ethics Committee Approval**

Muğla Sıtkı Koçman University Human Research Ethics Committee. Ethics Committee Number: 200236

## **Consent to participate**

Approval was obtained from the parent or legal guardian of each case participating in the study.

## **Statistical analysis**

IBM SPSS version 20.0 software (IBM Corp, Armonk, NY, USA) was used for statistical evaluation and normal distribution was checked using Kolmogorov-Smirnov test. Data are presented as mean  $\pm$  standard deviation. Statistical comparison of the right and left OBV values and the depth of the right and left olfactory sulcus was made using the paired t test. Independent-sample t test was used to evaluate the statistical differences between groups formed by considering gender, while one-way ANOVA test was used to evaluate the statistical differences between groups formed according to age. Multiple comparisons were made with the Tukey test and a P value of 0.05 was considered statistically significant.

## **RESULTS**

A total of 190 patients (95 males, 95 females) were included in the study. The mean age was  $9.9 \pm 7.5$  months for the infantile period,  $4.5 \pm 1.3$  years for early childhood,  $9.3 \pm 1.7$  years for childhood and  $15.2 \pm 1.7$  years for adolescence. The OBV was  $42.03 \pm 5.96$  (range 29,2-57,6)  $\text{mm}^3$  on the right and  $42.33 \pm 6.06$  (range 28,8-62,4)  $\text{mm}^3$  on the left side. There was no statistical difference between right and left side OBV ( $P > 0.167$ ). Mean, right and left OBV was found to be slightly larger in male children than female children ( $P = 0.015$ ,  $P = 0.033$  and  $P = 0.010$ , respectively) (Table 1). OSD values were  $8.34 \pm 0.92$  on the right and  $8.32 \pm 0.89$  mm on the left. There was no statistical difference between right and left in terms of OSD ( $P > 0.481$ ). There was no statistical difference between the genders for mean, right and left OSD ( $P = 0.559$ ,  $P = 0.536$  and  $P = 0.598$ , respectively) (Table I).

The distribution of mean OBV and OSD according to age groups are given in Table 2. Among the age groups, the values of the 3rd and 4th groups in terms of mean, right and left OBV were higher than the other two groups (Table II) ( $P < 0.001$ ). In terms of OSD, mean, right and left values were higher in group 2, 3 and 4 than group one (Table II) ( $P < 0.001$ ).

## DISCUSSION

There are several important results of our study. First, in the pediatric age group, the olfactory bulb volume increases as the age increases, but the most significant volume increase is in the 7-12 age group. Second, OSD is lower in the infantile patient group (1-24 months) compared to other pediatric age groups. After 3 years of age, there is no statistically significant change in the depth of the olfactory sulcus until the age of 18. Third, there was no statistically significant difference in OSD measurements based on gender in the normal healthy pediatric population, but OBV was slightly larger in male children than in female children.

MR imaging method has been used successfully in adults to analyze the normal anatomy of OBs [4, 6, 12, 20, 23]. In the study conducted by Schneider et al, Cranial MRI examinations of 121 pediatric cases aged between 1 and 19.6 years were retrospectively re-evaluated in order to detect the maturation of the olfactory bulb. Three anatomical patterns have been described defining different anatomical shapes for the olfactory bulb. Whatever the anatomical shape of the olfactory bulbs, they found that the gradual rearrangement of the peripheral neuronal layers and central structures of the bulb resulted in an adult-like appearance in all children at the end of the second year at the latest, in parallel with the maturation changes of the cerebral white matter [18]. Therefore, in our study, we grouped pediatric individuals of the first 2 years of age separately. However, we found that OB volume increased minimally in pediatric individuals aged 3-6 years compared to the first 2-year-old case group. We found the olfactory sulcus depth to be lower in the first 2-year-old pediatric group compared to the other three pediatric groups. This finding supports this study by Schneider et al on olfactory maturation.

In a study conducted by Croy et al on 27 depressed female individuals, 15 of whom were maltreated during childhood, the OB volume measured in individuals who were maltreated during childhood was found to be lower than those who were not exposed to childhood maltreatment [3]. In the first hypothesis they put forward for this result; It suggests that major stress exposure in childhood affects neurogenesis in human OB, as previously demonstrated in animal studies [7]. For these reasons, we think that, as in our study, it is important to know the normal OB volume and OSD measurement intervals in pediatric individuals to determine the connection between the abnormalities that may occur in adulthood and the pediatric period.

In a study conducted by Hummel et al on 87 pediatric individuals aged between 1 and 17 years without olfactory dysfunction (mean =  $8 \pm 5.5$  years, 46 boys and 41 girls), it was

found that OB volume and olfactory function increased with age [9]. In this study, OB volumes of male children (left: 71 mm<sup>3</sup>, right: 68 mm<sup>3</sup>) were found to be larger than female children (left: 65, right: 66 mm<sup>3</sup>). It was also found that for both boys and girls, the right and left OB volumes gradually increased from the age of 1 year. According to the study, the average OB volume for 1 year old boys is; left: 65, right: 64 mm<sup>3</sup>, mean OB volume for girls: left: 61, right: 62 mm<sup>3</sup>. When the mean OB volume was evaluated in 17 years old pediatric individuals, in boys: left: 79 mm<sup>3</sup>, right: 77 mm<sup>3</sup>; in girls: left: 73 mm<sup>3</sup>, right: 71 mm<sup>3</sup>. As a result of our study, OBV was found to be slightly higher in boys compared to girls, similar to the study of Hummel et al. However, although OBV increased gradually with age, it was found that the statistically more significant increase in OB volume was between the ages of 7-12, regardless of gender.

In studies conducted in patients with congenital anosmia and psychiatric disorders such as schizophrenia or psychosis, OSD was found to be lower than normal [9, 14, 21, 22]. Although standard values for the depth of the olfactory sulcus have been published mostly for adults, few studies have published standard values for the pediatric age group. In the study conducted by Smitka et al on 40 normosmic children aged between 6 and 18 years, it was found that OSD was 8 mm and above in all children over 9 years old [19]. It was stated that the recommended cut-off value of 8 mm, which indicates anosmia, can be used safely for children aged 9 years and above, and different limit values should be considered for children aged 8 years and under. In the study conducted by Huart et al in 106 individuals (36 anosmic individuals and 70 healthy individuals) aged between 7 and 79 years, sulcus depth below 8 mm was found to be an important indicator for the development of anosmia [8].

The first study in the literature examining the age-related change of both OSD and OBV in healthy pediatric individuals was conducted by Şahin et al. A total of 90 pediatric patients aged between 3 and 17 years were included in this study and a 1.5 tesla MRI device was used [16]. Our study is fundamentally different from 3 aspects according to the study of Şahin et al. The first is that healthy pediatric individuals in the 1 month-2 age group were included in the study and the study was conducted with 190 individuals, the second is the use of 3 Tesla MRI device and the third is that the OBV measurement method is different. Thus, the change in OBV and OSD in all pediatric age groups between 1 month and 17 years was examined. Studies including OSD and OBV measurements of healthy pediatric individuals in the literature are summarized comparatively in Table III.

According to our research, our study is the first study to separately show the development and change of the olfactory sulcus depth for 4 separate periods after birth until

the age of 18 in healthy pediatric individuals. It was found that OSD gradually increased with age in both healthy male and female individuals in the pediatric age group. The infantile group(0-24 months) had the lowest OSD and the mean OSD in this group was found to be less than 8 mm. For 3 years and above, mean OSD was over 8 mm for each age group. Another difference of our study from other studies is that the images were obtained with a 3T MR scanner. We think that we may have obtained more accurate results since 3 T MR images provide clearer and thinner-slice images with higher resolution.

Our study had some limitations. The first of these is that our study was retrospective and there was no evaluation of olfactory function. In addition, inter-observer variability was not taken into account in our study. Another limitation is that some of the individuals participating in the study were very young in age and the patient backgrounds were obtained from the hospital information system.

## CONCLUSIONS

In conclusion, there are still very few studies showing the development of OBV and OSD with age and time changes considering gender for normal healthy pediatric individuals. We think that more studies should be done on this subject, since these data show differences in both the pediatric age group and adults according to age and that OBV and OSD can be an indicator of the development of olfactory dysfunction. Therefore, within the pediatric age group, normal values should be calculated considering age and gender.

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**Table I.** The distribution of age, mean and both sides olfactory bulb volume (OBV) and olfactory sulcus depth in according to sexes.

	Group A (n=95)	Group B (n=95)	P value
OBV (mm <sup>3</sup> )			
Mean	41.15±5.32	43.20±6.15	0.015
Right	41.11 ± 5.67	42.95 ± 6.14	0.033
Left	41.20 ± 5.35	43.45 ± 6.52	0.010
OSD (mm)			
Mean	8.37±0.92	8.29±0.87	0.559
Right	8.38 ± 0.93	8.30± 0.92	0.536
Left	8.36 ± 0.93	8.30 ± 0.85	0.598

**Table II.** The distribution of age, mean and both sides olfactory bulb volume (OBV) and olfactory sulcus dept in according to age groups.

Data are n of participants, mean  $\pm$  SD.

	<b>0-2 years (n=40)</b>	<b>3-6 years (n=50)</b>	<b>7-12 years (n=50)</b>	<b>13-18 years (n=50)</b>
Age (years)	9.9 $\pm$ 7.5 ay	4.5 $\pm$ 1.3 yil	9.3 $\pm$ 1.7 yil	15.2 $\pm$ 1.7 yil
OBV (mm <sup>3</sup> )				
Mean	37.75 $\pm$ 4.27	39.26 $\pm$ 5.95	44.85 $\pm$ 5.01 <sup>a,b</sup>	44.96 $\pm$ 5.72 <sup>a,b</sup>
Right	37.70 $\pm$ 4.60	39.08 $\pm$ 5.98	44.72 $\pm$ 4.80 <sup>a,b</sup>	44.88 $\pm$ 6.07 <sup>a,b</sup>
Left	37.80 $\pm$ 4.34	39.44 $\pm$ 6.31	44.98 $\pm$ 5.55 <sup>a,b</sup>	45.03 $\pm$ 5.81 <sup>a,b</sup>
OSD (mm)				
Mean	7.54 $\pm$ 0.93	8.56 $\pm$ 0.78 <sup>a</sup>	8.30 $\pm$ 1.39 <sup>a</sup>	8.60 $\pm$ 0.78 <sup>a</sup>
Right	7.48 $\pm$ 0.96	8.58 $\pm$ 0.78 <sup>a</sup>	8.49 $\pm$ 0.71 <sup>a</sup>	8.64 $\pm$ 0.82 <sup>a</sup>
Left	7.60 $\pm$ 0.95	8.53 $\pm$ 0.81 <sup>a</sup>	8.45 $\pm$ 0.74 <sup>a</sup>	8.56 $\pm$ 0.77 <sup>a</sup>

<sup>a</sup>P<.001 compared with 0-2 years group (Oneway ANOVA-Tukey test).

<sup>b</sup>P<.001 compared with 3-6 years group(Oneway ANOVA-Tukey test).

**Table III. Comparison of OBV and OSD Studies in Healthy Pediatric Cases**

Comparison of OBV and OSD Studies in Healthy Pediatric Cases								
First Author	Year	Country	Measurement Method	N	Age (Years)	Magnetic Field (Tesla)	OBV (mm3)	OSD (mm)
Hummel T.	2011	France	AMIRA 3-D visualization and modeling system (Visage Imaging, Carlsbad, USA)	87	1-17 Years	1,5 Tesla	M:21-98, R:68, L:71 F:21-121, R:66, L:65	No measurement
Sahin S.	2020	Turkey	Semi-automatically method, Philips workstation	90	3-17 Years	1,5 Tesla	M:32,7-98,6 R:64, L: 65,3 F: 31,8-99,6 R:67,1 L:72	R: 8,85 (min 6 max 13,6) L: 8,8 (min 1,8 max 16)
Our Study	2020	Turkey	3D Slicer software (3D Slicer software ver. 4.2.2-1, USA)	190	1 Month-17 Years	3 Tesla	M:30,1-62,4 R:41,11 L:41,20 F: 29,2-55,2 R:42,95 L:43,45	R: 8.34 $\pm$ 0.92 L: 8,32 $\pm$ 0.89

**Figure 1.** The coronal T2-weighted image shows the olfactory bulb volume measurement and the olfactory sulcus depth measurement. A measurement example of olfactory sulcus depth (small hollow arrow) and a measurement example of olfactory bulb surface area (large hollow arrow).

