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NEURORADIOLOGY

ORIGINAL ARTICLE

Quantitative analysis of the olfactory system in pediatric epilepsy: a magnetic resonance imaging study

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PURPOSE

Olfactory dysfunction is a well-known complication in epilepsy. Studies have demonstrated that olfactory bulb volume (OBV), olfactory tract length (OTL), and olfactory sulcus depth (OSD) can be reliably evaluated using magnetic resonance imaging (MRI). In this study, we compared the OBV, OTL, and OSD values of children with epilepsy and those of healthy children (controls) of similar age. Our aim was to determine the presence of olfactory dysfunction in children with epilepsy and demonstrate the effects of the epilepsy type and treatment on olfactory function in these patients.

METHODS

Cranial MRI images of 36 patients with epilepsy and 108 controls (3–17 years) were evaluated. The patients with epilepsy were divided into groups according to the type of disease and treatment method. Subsequently, OBV and OSD were measured from the coronal section and OTL from the sagittal section. The OBV, OTL, and OSD values were compared between the epilepsy group, subgroups, and controls.

RESULTS

OBV was significantly reduced in the children with epilepsy compared with the control group ($P < 0.001$). No significant difference between the healthy children and those with epilepsy was determined in terms of OTL and OSD. Although OBV was moderately positively correlated with age in the control group ($r = 0.561$, $P < 0.001$), it was poorly correlated with age in children with epilepsy ($r = 0.393$, $P = 0.018$).

CONCLUSION

The results of our study indicate that OBV decreases in children with epilepsy, but epilepsy type and treatment method do not affect OBV, OTL, or OSD ($P > 0.05$).

KEYWORDS

Epilepsy, magnetic resonance imaging, olfactory bulb, olfactory sulcus, olfactory tract

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Epilepsy is a chronic neurological disease that affects people of all ages.[1] The incidence of epilepsy in children varies from 41 to 187 per 100,000, with approximately 30,000 children being diagnosed with epilepsy every year.[2] Olfactory abnormalities in epilepsy are well documented. Clinically, these abnormalities present as olfactory auras or olfactory performance deficits such as odor detection impairment.[3] The olfactory system consists of primary olfactory nerves in the nasal cavity, the olfactory bulb, olfactory tract, and connections extending to the central nervous system. The olfactory nerves traverse the cribriform plate and form olfactory bulbs intracranially, and the olfactory tracts connect the olfactory bulbs to the brain. The olfactory bulbs and tracts are located under the olfactory sulcus on the lower surface of the frontal lobe. Nerve fibers originate from the olfactory tract and extend to the amygdala, olfactory tubercle, and parahippocampal gyrus.[4] Olfactory bulb volume (OBV), olfactory tract length (OTL), and olfactory sulcus depth (OSD) can be reliably evaluated using magnetic resonance imaging (MRI),[5,6] and OBV is clinically important for measuring olfactory function.[7]

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To date, studies on the olfactory system in epilepsy have generally focused on adults;[3,8,9] however, few published studies relate to the imaging findings of the olfactory system (such as OBV measurement) in adults with epilepsy.[8,9] To the best of our knowledge, no study has provided a quantitative analysis of the olfactory system (such as OBV, OSD, or OTL measurement) in childhood epilepsy. Therefore, in the present study, we aim to compare the quantitative measurements of olfactory anatomical structures (OBV, OSD, and OTL) between patients diagnosed with childhood epilepsy and healthy controls.

Methods

Participants

This study had a retrospective design (local ethics committee approval no: 2019/2-28) and involved 36 patients with epilepsy who underwent cranial MRI between January 2016 and August 2020. Informed consent was not obtained because the study was in a retrospective design. Only patients diagnosed with primary epilepsy were included in the study group. Patients with uncontrolled epilepsy, intellectual disability, or a history of hypoxic ischemic encephalopathy, trauma, meningoencephalitis, prematurity, endocrinopathy, metabolic disease, or neurodegenerative disease were excluded. Cases with inadequate MRI images were also excluded. Patients with normal brain MRI reports were included in the study. The patients that met the study criteria were divided into three groups according to the International League Against Epilepsy 2017 criteria: generalized onset, focal onset, and unclassified. The generalized-onset group contained 23 patients, the focal-onset group 8 patients, and the unclassified group 5 patients.

Main points

- There is a correlation between decreased olfactory bulb volume (OBV) and the presence of some neurodegenerative diseases, such as dementia and Alzheimer disease. To date, studies on the olfactory system in epilepsy have focused on adults.
- A quantitative analysis of the olfactory system can be reliably undertaken using magnetic resonance imaging. In this study, OBV values of pediatric patients with epilepsy were decreased.
- The decrease in OBV in children with epilepsy reflects not only the olfactory function of OBV but also the destructive effect of childhood epilepsy on the nervous system.

The patients were also categorized according to the treatment they were receiving: those in remission who were not receiving any medical treatment at that time (n = 9), those using a single antiepileptic agent (n = 20), and those using two or more antiepileptic agents (n = 7). The control group consisted of 108 children aged 3 to 17 years who underwent brain MRI for reasons other than epilepsy (e.g., tension-type headache, transient non-specific benign vertigo attacks, or somatization) and were reported to have normal findings. Patients and controls were divided into three age-range groups as follows: group 1, young children (3–6 years); group 2, children (7–11 years); and group 3, adolescents (12–17 years). Patients and controls were compared in these three groups.

Magnetic resonance imaging studies

The MRI studies were evaluated by two radiologists with 12- and 10-years' experience. The radiologists did not know which group the studies belonged to. Two radiologists performed the measurements separately, and the mean value was used for analysis. Images were obtained using a 1.5 T scanner (Achieva, Philips Medical Systems, Best, Netherlands) with a head coil. Images in the coronal section were obtained perpendicular to the cribriform plate. Examination sequences were composed of balanced fast-field echo (B-FFE) three-dimensional (3D) images in the coronal plane [repetition time (TR), 6.5 ms; echo time (TE), 3.4 ms; field of view (FOV) 180 180 mm; number of signals averaged (NSA), 2; thickness, 1 mm; gap, 0 mm; slices, 75; matrix, 308 308 mm] and sagittal 3D T1-weighted images (TR, 8.2 ms; TE, 4.0 ms; FOV, 140 156 mm; NSA, 4; thickness, 1.2 mm; gap, 0.2 mm; slices, 40; matrix, 252 278 mm). The MRI scan time was 4–5 min.

Image analysis

OBV, OTL, and OSD were measured in all patients. On the coronal B-FFE 3D images, the olfactory bulb was visualized as a hypointense round or ovoid structure surrounded by cerebrospinal fluid superior to the anterior cribriform plate (Figures 1, 2). The relatively abrupt change in diameter defined the proximal border of the bulb (on coronal plane B-FFE 3D images). Volume measurements were obtained using manual segmentation based on the contour stack principle and calculated using the Philips Extended MR workspace (version 2.6.3.5) post-processing software package (Philips Medical Systems). OSD was measured on coronal B-FFE 3D images, and the maximum depth was recorded (Figure 3). Olfactory tract measurements were performed on the plane on which the olfactory tract was most clearly seen on sagittal 3D T1 reformatted images (Figure 4).

Statistical analysis

To perform the statistical analysis, SPSS v25.0 software was used. The Kolmogorov–Smirnov test was used to determine whether the data were distributed normally. The control and epilepsy groups were compared using the independent sample t-test. The Mann–Whitney U test was used to compare the epilepsy and control groups in small groups. The Kruskal–Wallis test was used for a comparison of more than two groups in terms of OBV, OTL, and OSD values. When parametric tests were used, mean and standard deviation (SD) values were given, and when non-parametric tests were used, median, minimum, and maximum values were given. The demographic characteristics of the epilepsy and control groups are presented as mean ± SD, and categorical variables are expressed as counts and percentages. The relationship between OBV, OSD, and OTL measurements and age was assessed using Pearson's correlation coefficient.

The intraclass correlation coefficient (ICC) was used in the study because of its ability to compare quantitative measurements among observers. The ICC test was calculated using a two-way random absolute single measurement model with a 95% confidence interval. Interobserver agreement in OBV, OSD, and OTL measurements was evaluated using Bland–Altman plots, which were produced through SPSS software. The average difference and 95% limits of agreement (mean difference ± 1.96 SD) are specified. The statistically significant level was accepted as $P < 0.05$.

Results

The ICC, indicating agreement in interobserver measurements, was good to excellent and ranged from 0.73 to 0.96 (Table 1). Of the cases diagnosed with epilepsy, 20 were boys (55%) and 16 (45%) were girls, and the mean age was 7.53 ± 3.60 years. The control group consisted of 108 cases, of which 60 were boys (55%) and 48 were girls (45%) (mean age 8.23 ± 4.55). OBV was significantly decreased in patients with epilepsy compared with the control group (Table 2), but no significant difference was identified in terms of right and left OTL and OSD between the epilepsy and control groups ($P = 0.188$, 0.726 and $P = 0.920$, 0.845, respectively).

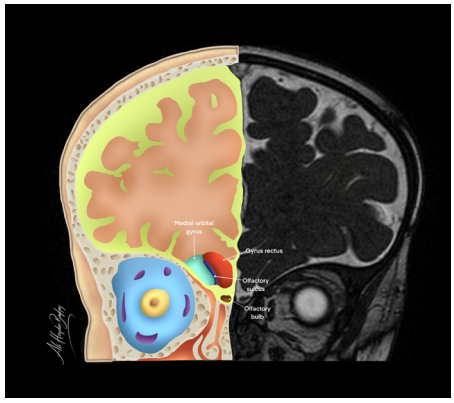

Figure 1. Illustration of the olfactory system on coronal plane magnetic resonance imaging. The medial orbital gyrus (green area), gyrus rectus (red area), olfactory sulcus (blue area), and olfactory bulb (brown area) are depicted at the side of the illustration.

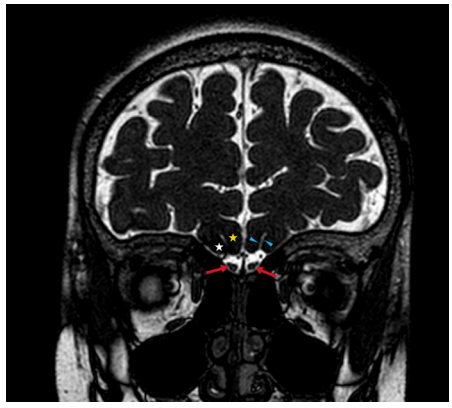

Figure 2. Coronal three-dimensional balanced fast-field echo magnetic resonance images of a 6-year-old girl showing the right and left olfactory bulb as a hypointense ovoid structure (arrows). The olfactory sulcus is displayed as a hyperintense line between the medial orbital gyrus (white star) and gyrus rectus (yellow star). Note the hyperintense cerebrospinal fluid surrounding the olfactory bulbs.

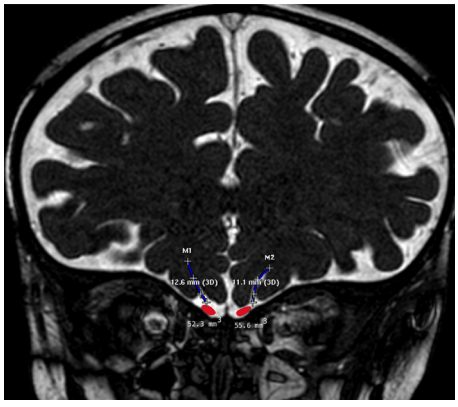

Figure 3. Olfactory bulbs (red area) and olfactory sulcus (blue line) are shown on coronal three-dimensional (3D) balanced fast-field echo magnetic resonance imaging. A semi-automatic measurement of the olfactory bulb volume using manual segmentation and multiplanar reformatting on the 3D workstation. To minimize the possibility of errors in volumetric measurements, the images were magnified as much as possible. The volumes are given in mm^3, and the line measurements are given in mm.

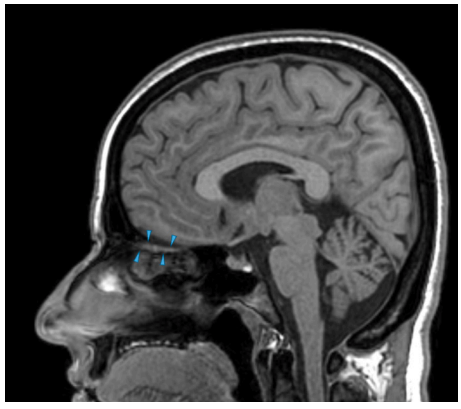

Figure 4. A sagittal T1-weighted magnetic resonance image revealing the boundaries of the right olfactory tract (arrowheads).

Table 1. Intraclass correlation coefficient estimates of two observers

Variables	ICC (95% CI)
Right OBV	0.89 (0.81–0.93)
Left OBV	0.96 (0.94–0.97)
Total OBV	0.96 (0.94–0.97)
Right OTL	0.90 (0.63–0.96)
Left OTL	0.88 (0.72–0.94)
Right OSD	0.73 (0.57–0.83)
Left OSD	0.84 (0.73–0.90)

OBV, olfactory bulb volume; OTL, olfactory tract length; OSD, olfactory sulcus depth; CI, confidence interval; ICC, intraclass correlation coefficient.

In addition, no significant difference was detected when the right and left OSD values were compared within the epilepsy and control groups ($P = 0.334$, $P = 0.445$, respectively) nor between the right and left OTL in the epilepsy and control groups ($P = 0.947$, $P = 0.402$, respectively). Pearson's correlation coefficients were calculated, and a weak positive correlation was observed between age and OBV in the epilepsy group ($r = 0.393$, $P = 0.018$), and there was a moderate positive correlation between OBV and age in the control group ($r = 0.561$, $P < 0.001$). The right and left OTL and OSD values were not correlated with age ($r = 0.095$; $P = 0.256$, $r = 0.001$; $P = 0.993$, $r = 0.921$; $P = 0.275$, $r = 0.583$; $P = 0.488$, respectively). The right and left OBV, OTL, and OSD values did not significantly differ according to sex in either group (patients: $P = 0.445$, $P = 0.585$, $P = 0.432$, $P = 0.266$, $P = 0.504$, $P = 0.581$; controls: $P = 0.112$, $P = 0.990$, $P = 0.643$, $P = 0.975$, $P = 0.681$, $P = 0.922$, respectively).

No significant difference in OBV, OTL, and OSD was identified among the patients with generalized-onset, focal-onset, or unclassifiable epilepsy (Table 3). Furthermore, no significant difference was found in these three parameters among the single therapy, multiple therapy, and non-therapy groups (Table 4). When all age groups were compared, there was no significant relationship between the right and left OTL and OSD values of the patient and control groups ($P = 0.643$, $P = 0.921$, $P = 0.141$, $P = 0.143$, respectively). However, OBV values decreased in the epilepsy group in all age groups (Table 5). Bland–Altman graphics representing the relationship between the differences in measurements and the mean values identified by the two radiologists are presented in Figures 5 and 6.

Discussion

Olfactory deficits (odor identification, recognition memory, discrimination, and perception threshold) are more prominent in patients with epilepsy than in healthy individuals.[3] Khurshid et al.[3] conducted a meta-analysis on epilepsy and smell by screening 21 articles, revealing that olfactory deficits varied according to epilepsy types and were most prominent in temporal and mixed frontal lobe epilepsy. Impaired smell identification in patients with temporal lobe epilepsy before seizures, as well as those with a history of temporal lobectomy, demonstrates the effect of the temporal lobe on the sense of smell.[3]

Table 2. Comparison of the epilepsy and control groups

Variables	Epilepsy (n = 36) (mean ± SD)	Control (n = 108) (mean ± SD)	*P*
Right OBV	54.60 ± 11.29	66.30 ± 13.44	<0.001
Left OBV	52.66 ± 10.82	66.25 ± 17.13	<0.001
Total OBV	106.61 ± 16.69	132.55 ± 28.27	<0.001
Right OTL	24.30 ± 3.08	25.16 ± 3.43	0.188
Left OTL	24.55 ± 3.29	24.17 ± 3.19	0.726
Right OSD	10.09 ± 1.98	10.13 ± 1.65	0.920
Left OSD	9.95 ± 1.64	10.02 ± 1.89	0.845

Independent two samples t-test was used. SD, standard deviation; OBV, olfactory bulb volume; OTL, olfactory tract length; OSD, olfactory sulcus depth.

Table 3. Comparison of the parameters among the epilepsy subgroups according to seizure type

Variables	Generalized onset (n = 23) median (min–max)	Focal onset (n = 8) median (min–max)	Unclassified (n = 5) median (min–max)	*P*
Right OBV	53.44 (37.08–65.55)	56.70 (52.44–70.09)	47.39 (41.29–62.99)	0.193
Left OBV	51.87 (29.08–74.68)	54.43 (37.96–74.65)	54.73 (37.39–63.79)	0.754
Total OBV	102.93 (71.16–133.16)	114.96 (90.40–140.12)	102.50 (78.68–124.65)	0.367
Right OTL	23.60 (18.13–30.14)	26.80 (21.58–29.80)	23.32 (20.96–26.46)	0.161
Left OTL	25.35 (17.89–29.86)	23.91 (21.62–27.52)	22.53 (19.57–25.93)	0.337
Right OSD	9.52 (6.32–14.20)	10.72 (9.12–13.04)	11.09 (8.86–11.67)	0.320
Left OSD	9.93 (6.31–14.30)	9.60 (8.14–13.57)	10.19 (8.92–11.61)	0.808

OBV, olfactory bulb volume; OTL, olfactory tract length; OSD, olfactory sulcus depth (Kruskal–Wallis test was used), min, minimum; max, maximum

Table 4. Comparison of the parameters among the epilepsy subgroups according to treatment

Variables	Single antiepileptic (n = 20) median (min–max)	Multiple antiepileptics (n = 9) median (min–max)	No therapy (n = 7) median (min–max)	*P*
Right OBV	57.79 (37.08–70.09)	50.41 (41.29–62.81)	53.45 (46.45–63.32)	0.214
Left OBV	51.90 (39.72–74.68)	51.87 (29.08–66.72)	52.24 (41.32–63.79)	0.729
Total OBV	106.54 (76.80–140.12)	102.12 (71.16–129.42)	106.69 (92.08–124.65)	0.397
Right OTL	23.51 (18.13–29.80)	25.87 (19.88–30.14)	23.61 (21.71–27.13)	0.670
Left OTL	24.70 (17.89–29.74)	24.08 (18.63–29.86)	24.26 (20.68–28.18)	0.728
Right OSD	10.87 (7.32–14.20)	9.67 (6.82–11.24)	9.01 (6.32–13.04)	0.418
Left OSD	10.01 (6.31–14.30)	8.98 (6.73–11.56)	10.59 (8.92–13.57)	0.100

OBV, olfactory bulb volume; OTL, olfactory tract length; OSD, olfactory sulcus depth (Kruskal–Wallis test was used), min, minimum; max, maximum

Table 5. Comparison of epilepsy and control groups by age group

Age groups	Variables	Epilepsy (n = 14, 12, 10) median (min–max)	Control (n = 46, 31, 31) median (min–max)	*P*
3–6 years (group 1)	Right OBV	54.13 (37.08–63.32)	62.21 (35.87–85.79)	0.009
	Left OBV	47.70 (29.08–74.68)	59.34 (34.10–102.97)	0.009
	Total OBV	98.62 (71.16–133.16)	122.15 (73.51–188.76)	0.005
7–11 years (group 2)	Right OBV	55.23 (41.29–65.55)	63.37 (38.98–92.47)	0.009
	Left OBV	50.87 (37.39–74.65)	64.19 (41.19–95.46)	0.011
	Total OBV	106.51 (78.68–140.12)	126.51 (87.56–182.11)	0.002
12–17 years (group 3)	Right OBV	54.95 (41.17–70.09)	77.55 (51.40–98.74)	<0.001
	Left OBV	56.78(51.24–66.72)	75.66 (43.56–121.04)	0.004
	Total OBV	111.99 (95.39–129.53)	155.96 (94.95–205.51)	0.001

OBV, olfactory bulb volume, min, minimum; max, maximum

The olfactory bulb is the first key station that relays odor information from the periphery. It ends in the olfactory tract and is closely related to the olfactory sulcus in the frontal lobe. OBV is a criterion for evaluating olfactory function and is smaller in patients with anosmia than in those with hyposmia.[10] In patients with posttraumatic and postinfectious (as in sinusitis) odor loss, a significant correlation was reported between olfactory recovery and the initial OBV measurement (the more prominent the initial OBV, the more meaningful the improvement in olfactory function).[7] One study revealed that OBV varied according to age, and although there was no obvious difference in adults until the age of 40 years, OBV started to decrease in the 60–70-years age group.[7] In the same study, the OBV cut-off value was determined as 40 mm^3 for adults without smell dysfunction.[7]

In the only pediatric study, quantitative measurements of OBV, OTL, and OSD were performed in healthy children, and these values were observed to increase with age without sex difference.[11] OBV decreased in posttraumatic and postinfectious olfactory disorders, congenital anosmia, and neurodegenerative diseases (e.g., Parkinson, Alzheimer, and Behçet diseases).[5,7,12-15] In a study conducted on patients with mesial temporal lobe epilepsy, OBV was significantly lower in this group than in the control group, and the mean OBV of patients with hyposmia (epilepsy) was significantly lower than that of patients with normosmia.[9]

In an experimental study, the development of epilepsy was reported in mice in which olfactory bulbectomy had been performed.[16] In other studies, increased excitability in the amygdala was revealed after olfactory bulbectomy in mice.[17,18] These studies suggest that the olfactory bulb may play a role in suppressing epileptic discharges rather than being an epileptic focus. In humans, the presence of reflex epilepsy provoked by smell[19] suggests that the olfactory bulb may be involved in the etiopathogenesis of epilepsy.

Doğan et al.[13] reported that OBV decreased in Behçet disease, but they did not find a difference in OSD compared with the control group. OSD was reported to be lower than that of controls in certain diseases, such as schizophrenia, migraine, Parkinson disease, and major depression.[8,12,14,20-22] Although OBV has previously been reported to decrease in cases of olfactory dysfunction that develop because of upper respiratory tract infection and in patients with allergic rhinitis, in the same studies, no significant difference in OSD was observed compared with controls.[23,24] Few studies have been published on OTL. One study revealed that OTL is decreased in patients with essential tremor compared with controls.[25] Kumar et al.[26] induced olfactory hallucination in 11 children with focal epilepsy by stimulating the olfactory bulb or tract using subdural electrodes.

Although the olfactory nerve is a pure sensory nerve, it also exhibits volume loss in cases where extrapyramidal motor function is impaired, such as Parkinson disease, systemic diseases such as Behçet, psychosomatic disorders such as restless legs syndrome,[27] and neurogenic abnormal discharges such as epilepsy. Thus, in many systemic diseases in which olfactory function is not clinically impaired, OBV decreases or the olfactory system may be affected.

In this study, the OBV value increased with age in both children with epilepsy and healthy children, but this increase was lower in the epileptic group than in the control group. This result might indicate that the development of the olfactory bulb is slowed in children with epilepsy.

This study has certain limitations, such as its retrospective design, evaluation of cases based on medical files, absence of an evaluation of the olfactory aura or disease duration in patients with epilepsy, absence of odor testing, and the sample not including any patient with a history of epilepsy surgery.

In conclusion, the quantitative analysis of the olfactory system can be reliably undertaken using MRI. In this study, there was a decrease in the OBV values of pediatric patients with epilepsy. The literature suggests the presence of a correlation between reduced OBV and presence of neurodegenerative diseases, and OBV is not only associated with olfactory function but also reflects the devastating effect of diseases on the nervous system. Further research investigating different diseases in wider populations might better reveal the relationship between OBV and neurodegeneration.

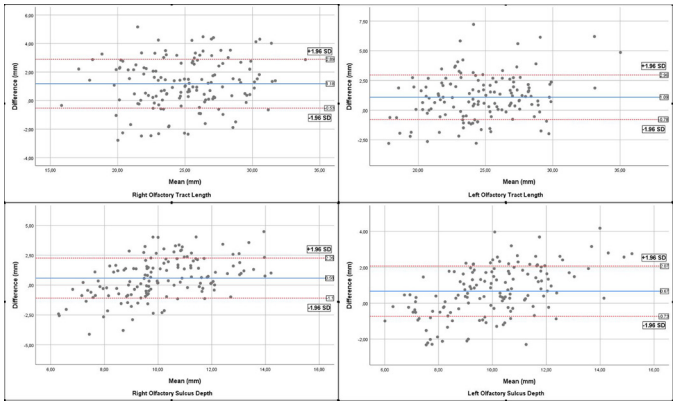

Figure 5. Bland–Altman graphics of the interobserver agreement for olfactory tract length and olfactory sulcus depth. The difference between the two observers is plotted on the y-axis and the mean value of the measurements on the x-axis. A continuous line indicates mean difference. Dashed upper and lower lines indicate the upper and lower limits of the 95% fit limits (mean ± variability estimate = 1.96 standard deviation).

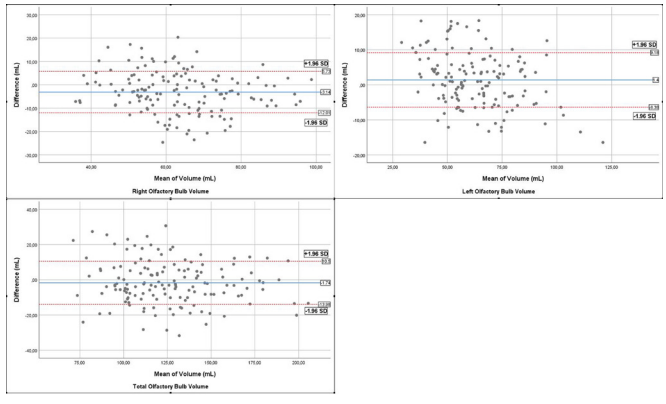

Figure 6. Bland–Altman graphics of the interobserver agreement for olfactory bulbus volumes. The difference between the two observers is plotted on the y-axis and the mean value of the measurements on the x-axis. A continuous line indicates mean difference. Dashed upper and lower lines indicate the upper and lower limits of the 95% fit limits (mean ± variability estimate = 1.96 standard deviation).

Conflict of interest disclosure

The authors declared no conflicts of interest.

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