

ORIGINAL STUDY

Vitamin D3 deficiency and smell regions in adolescents: an MRI evaluation

Serkan Tursun¹, Nuray Bayar Muluk², Adnan Özdemir³, Ziya Şencan²

¹Pediatrics Department, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey

²ENT Department, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey

³Radiology Department, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey

ABSTRACT

OBJECTIVES. We investigated the effect of vitamin D3 deficiency on peripheral and central odor centres by using cranial magnetic resonance imaging (MRI).

MATERIAL AND METHODS. In this retrospective study, cranial MRI images of 23 adolescents with vitamin D3 deficiency and 18 adolescents with normal vitamin D3 levels (≥ 20 ng/ml) were evaluated. Blood tests for vitamin D3, B12, hemoglobin and calcium levels were also taken from the database of our hospital. Peripheral odor centers, olfactory bulb (OB) volume and olfactory sulcus (OS) depth, and also central odor centers, insular gyrus and corpus amygdala area were measured on cranial MRI.

RESULTS. The insular gyrus and corpus amygdala area were not different between the study group with vitamin D3 deficiency and the control group ($p > 0.05$). There was no difference between OB volume of the study and control groups ($p > 0.05$). Although the right insular area was lower in girls than males ($p < 0.05$), there was no correlation between OB volume and gender ($p > 0.05$). Higher hemoglobin levels were related to higher OB volume on the right side ($p < 0.05$).

CONCLUSION. In the group with vitamin D3 deficiency, olfactory bulb volume of the left side was asymmetrically larger than the one on the right side. Therefore, the measurements of vitamin D3 should be performed in adolescents, and the patients with the vitamin D3 levels of < 20 ng/ml should be supplemented with medical treatment and reinforcing vitamin D synthesis by the exposure of sunlight more.

KEYWORDS: vitamin D3, adolescents, smell, MRI, olfactory bulb volume, olfactory sulcus depth.

INTRODUCTION

Vitamin D3 is a fat-soluble vitamin that acts as a steroid hormone. In addition to the importance of calcium and phosphorus metabolism and hence bone homeostasis, the deficiency of vitamin D3, which has receptors in various tissues such as the immune system, brain, heart, adipose tissue and pancreas, is associated with autoimmune diseases, various cancers, cardiovascular and metabolic diseases¹⁻⁵. Moreover, vitamin D3 deficiency is associated with a wide range of neuropsychiatric disorders and neurodegenerative diseases^{6,7}.

In recent years, there are an increasing number of studies that provide important information about the mechanisms of action of vitamin D3 on the neurological system,

especially on the brain⁸⁻¹⁰. However, publications showing the relationship of olfactory nerve functions with vitamin D3 remained only at the level of the case report¹¹.

This study aimed to investigate the effect of vitamin D3 deficiency on peripheral (olfactory bulb volume and olfactory sulcus depth) and central odor centers (insular gyrus and corpus amygdala area) by using MRI images in the evaluation of odor pathways.

MATERIAL AND METHODS

This retrospective study was conducted in Pediatrics, Otorhinolaryngology and Radiology Departments of Kırıkkale

Corresponding author: Dr. Nuray Bayar Muluk, ENT Department, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey

Address: Birlik Mahallesi, Zirvekent 2. Etap Sitesi, C-3 blok, No: 6-3/43, 06610, Çankaya / Ankara, Turkey

ORCID: <https://orcid.org/0000-0003-3602-9289>

e-mail: nuray.bayar@yahoo.com; nurayb@hotmail.com

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University Faculty of Medicine. The rules of Declaration of Helsinki were followed. The radiology Department of Kırkkale University Faculty of Medicine database for cranial MRI was used. "Kırkkale University Non-invasive Research Ethics Committee" approval was taken (Date: 26.06.2019, Number:2019/06/20).

Subjects

This study was performed retrospectively. Cranial MRI images of 41 adolescents were screened and selected from the PACS system of our hospital from the current time to the past and their results were reported as normal.

Group 1, the study group, consisted of 23 children (4

males and 19 females) with 25-dihydroxy vitamin D₃ (25(OH)₂D₃) deficiency. 25(OH)₂D₃ values were also received from our hospital's database. For 25(OH)₂D₃ values ≥ 20 ng/ml was considered as normal¹², and lower values were considered as 25(OH)₂D₃ deficiency¹². The mean ages were 16.14 ± 0.67 years (ranged from 15 to 17).

The control group (Group 2) consisted of 18 children without 25(OH)₂D₃ deficiency (8 males, 10 females), with normal cranial MRI results in our Hospital's PACS system. In these patients, the MRI was taken for vertigo or cephalgia and the results were reported as normal. They were selected by screening the PACS system from the current time to the

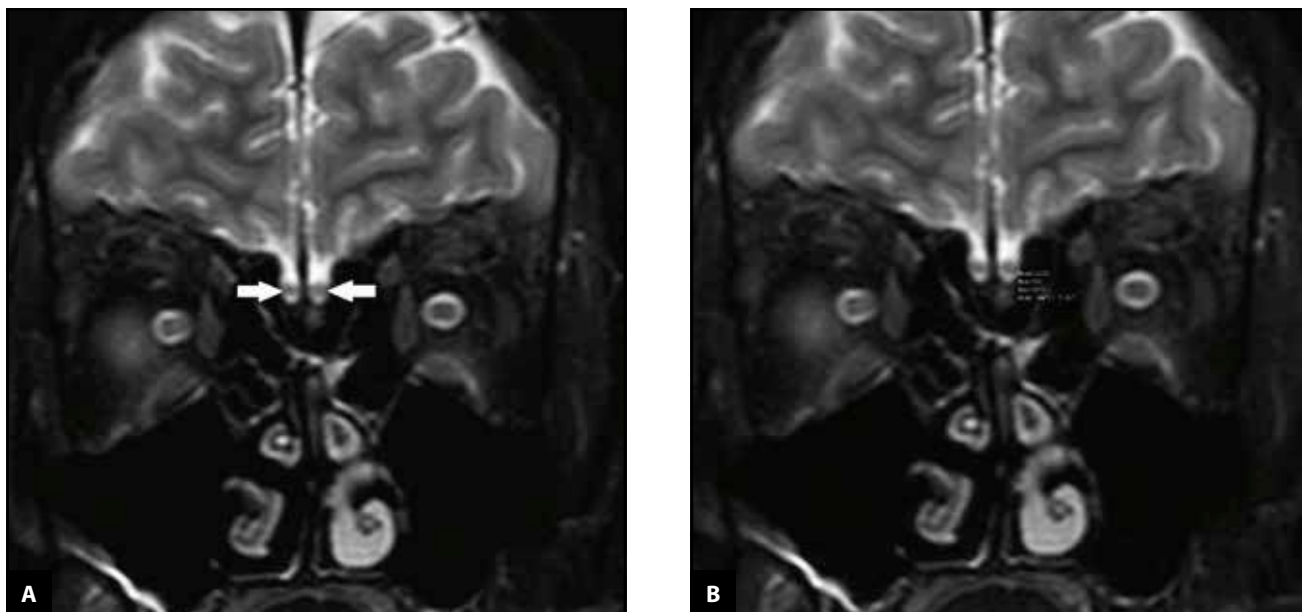


Figure 1. T2-weighted coronal MRI: **A.** olfactory bulbs (white arrows) are presented; **B.** the measurement of the olfactory bulb is shown.

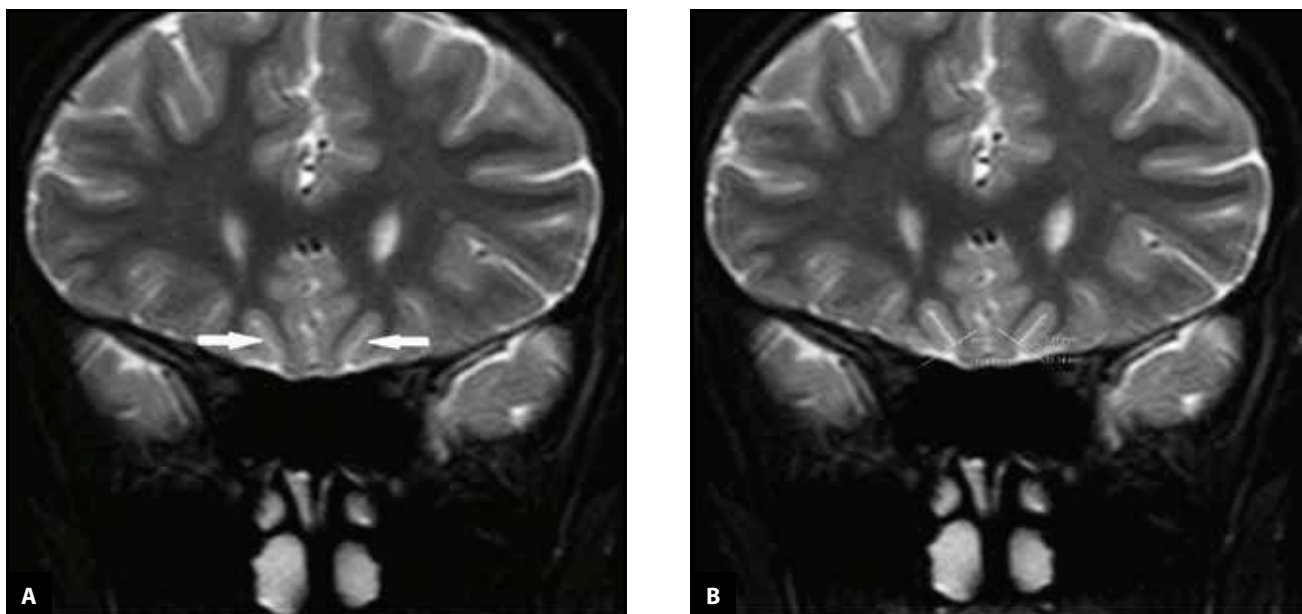


Figure 2. Female patient in her teens, in T2-weighted coronal MRI: **A.** olfactory sulcus (white arrows) is presented; **B.** the measurement of the olfactory sulcus is shown.

past. The mean ages were 16.44 ± 0.72 years (ranged from 14 to 17.5).

Subjects with sinonasal infections or CSF leak, tumor, polypoid, marked facial or septal deformity, history of surgery or trauma, hyperparathyroidism, dementia, Parkinson and Alzheimer diseases, epilepsy, multiple sclerosis or chronic renal failure were not included in the study.

Blood tests

In both groups, $25(\text{OH})_2\text{D}_3$ (ng/mL), Vitamin B12 (pg/ml), Hemoglobin (g/dL), Platelet count, TSH ($\mu\text{U}/\text{mL}$), Folic acid (ng/ml), Ferritin ($\mu\text{g}/\text{L}$), Calcium (mg/dL) and Phosphorus (mg/dL) results in the blood were taken from

the database of our hospital.

Cranial MRI measurements

MRI scans were conducted with a 1.5 Tesla Philips MRI machine (Philips MRI Systems, Achieva Release 3.2 Level 2013-10-21, Philips Medical Systems Nederland B.V.), utilizing a cranial coil. T1-weighted images were acquired in the axial orientation with the following parameters: TR msn/TE msn; 596/15, FOV 230x183 mm, and matrix 256x205 mm. Additionally, T2-weighted images were obtained in the coronal orientation with the following settings: TR msn/TE msn; 6557/100, FOV 220x175 mm, and matrix 224x165 mm. The slice thickness was 5 mm with a 1-mm gap between intersec-

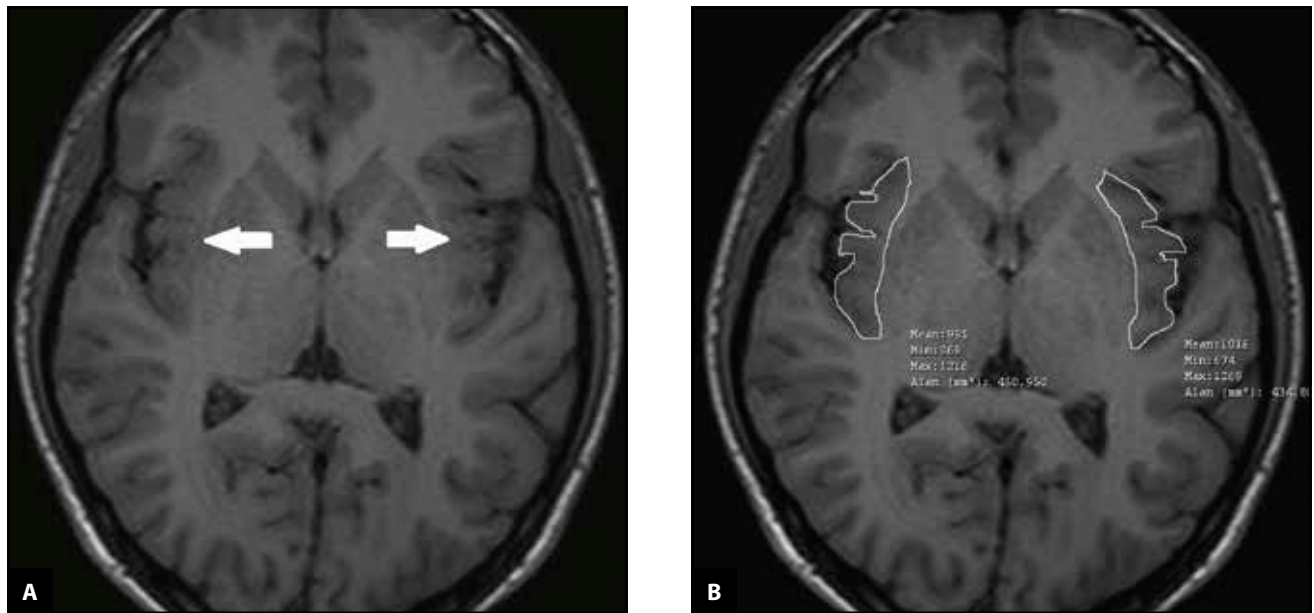


Figure 3. T1-weighted axial MRI: **A.** both insular gyri (white arrows) are presented; **B.** the measurement of both insular gyri is shown.

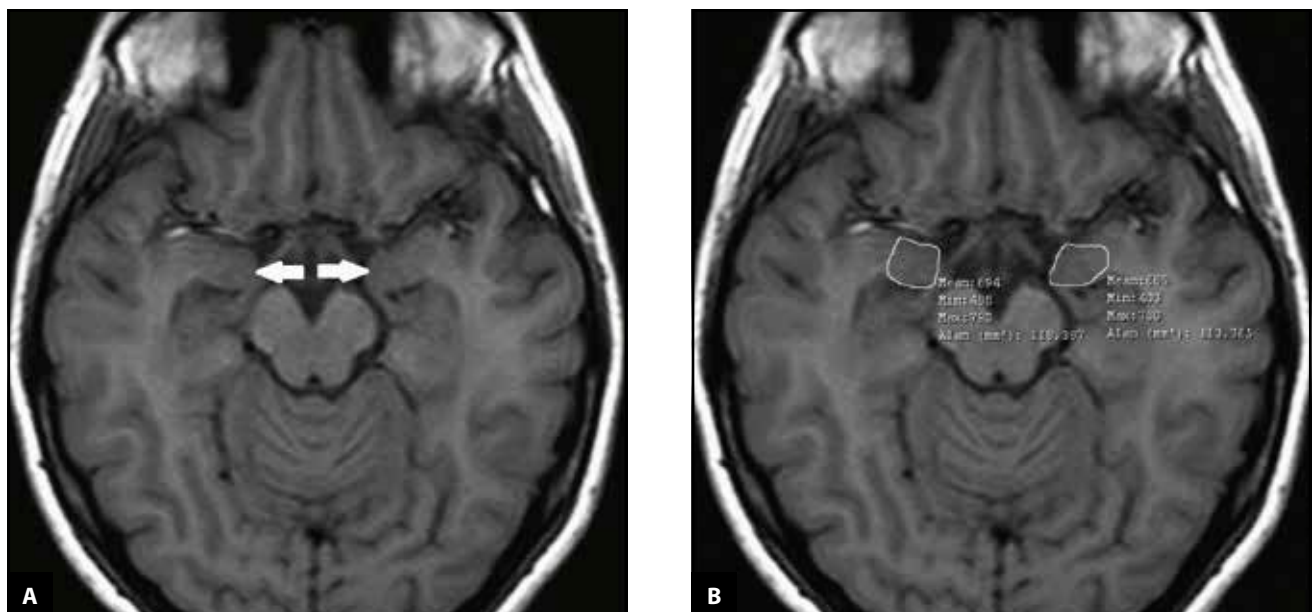


Figure 4. In an adolescent female patient, in T1-weighted axial MRI: **A.** both corpus amygdalas (white arrows) are presented; **B.** the measurement of both corpus amygdalas is shown.

Table 1. Blood test results of the Group 1 and 2.

	Group 1 (Vitamin D3 deficiency) (n=23)			Group 2 (Control group) (n=18)			p*
	Mean	Median	Std. Dev.	Mean	Median	Std. Dev.	
25(OH)₂D₃ (ng/mL)	11.73	11.21	4.83	28.79	26.13	7.12	0.000
Vitamin B12 (pg/ml)	250.67	255.65	85.22	329.90	267.70	190.20	0.444
Hemoglobin (g/dL)	13.95	13.95	1.30	14.60	14.50	1.14	0.086
Platelet	250.72	241.00	61.57	264.44	263.00	51.61	0.438
TSH (μU/mL)	2.28	2.36	0.736	2.62	2.52	1.04	0.482
Folic acid (ng/ml)	6.20	6.08	2.26	7.03	6.92	2.84	0.342
Ferritin (μg/L)	33.87	29.23	25.76	43.90	33.00	27.89	0.215
Calcium (mg/dL)	9.62	9.60	0.36	9.95	9.98	0.42	0.029
Phosphorus (mg/dL)	3.77	3.79	0.44	3.97	3.77	0.75	0.922

*p-value shows the Mann Whitney U test

tions, and 25-30 coronal sections were acquired¹³.

Measurement results were obtained from coronal T2-weighted SPIR images for olfactory bulb (OB) volume (Figure 1a-b) and olfactory sulcus (OS) depth (Figure 2a-b), axial T1-weighted images for insular gyrus area (Figure 3a-b) and the corpus amygdala area (Figure 4a-b)¹⁴. All measurements were evaluated by a single radiologist (A.Ö.).

Peripheral regions of smell

The assessment of olfactory bulb (OB) volume involved the utilization of coronal T2-weighted SPIR sequences. In a sequential manner from front to back, the olfactory bulb's distinct features were clearly discerned within the images. The surface area of the OB was then manually measured in square millimeters using an electronic cursor, and subsequently, the volume was computed by multiplying this measurement by the slice thickness, expressed in cubic millimeters¹⁴⁻¹⁶.

Regarding the measurement of olfactory sulcus (OS) depth, the procedure entailed utilizing the coronal T2-weighted SPIR sequence. A virtual tangent line was drawn extending from the inferior orbital gyrus to the gyrus recti in the posterior region of the orbit. From this tangent line, a perpendicular line was then drawn, extending to the deepest point within the OS. The length of this line provided the measurement for the depth of the olfactory sulcus (OS) in millimeters¹⁴⁻¹⁶.

Central regions of the smell

The area of the insular gyrus was determined in the sections where it exhibited its maximum visibility. This involved conducting measurements on images that displayed both the head of the caudate nucleus and the putamen^{17,18}.

Similarly, the area of the corpus amygdala in square millimeters (mm²) was assessed within the sections where its maximum presence was observed^{17,18}.

Statistical Analysis

The statistical analysis was performed with SPSS for Windows 16.0 (SPSS, INC, an IBM Company, Chicago, Illinois). Chi-square test, Mann Whitney U test, Wilcoxon Signed Ranks test and Spearman's correlation rho efficient test were used. P-value < 0.05 was considered as statistically significant.

RESULTS

Blood test results of the Group 1 and 2 were shown in Table 1. 25(OH)₂D₃ level was 11.73±4.83 ng/mL in Group 1 and 28.79±7.12 ng/mL in Group 2 (p<0.05). In both groups, the other blood test results (Vitamin B12, Hemoglobin, platelet, TSH, Folic acid, Ferritin, Calcium and Phosphorus) were in normal limits (Table 1). Except for calcium, there were no significant differences between groups (p>0.05). Calcium results of Group 1 (9.62±0.36 mg/dl) were significantly lower than those in Group 2 (9.95±0.42 mg/dl) (p<0.05).

Measurement results for olfactory bulb volume, olfactory sulcus depth, insular gyrus area and corpus amygdala area were shown in Table 2.

Olfactory bulb (OB) volume

Comparing the OB volumes between the two groups, we found no significant statistical difference (p>0.05). In Group 1, the study group, we observed that the left OB volume was higher than the one of the right side (p<0.05) (Table 2).

Olfactory sulcus (OS) depth

OS depth values of the study group, Group 1, were not different from the statistical point of view when compared to the values in Group 2 (p>0.05). In comparing the right and left sides, OS depth values were not different in Group 1; with the same observation for

Table 2. Measurement results for olfactory bulb volume, olfactory sulcus depth, insular gyrus area and corpus amygdala area.

		Group 1 (Vitamin D deficiency) (n=23)			Group 2 (Control group) (n=18)			p*
		Mean	Median	Std. Dev.	Mean	Median	Std. Dev.	
Age		16.14	16.00	0.67	16.44	16.75	0.72	0.166
Measurements results								
Olfactory bulb (OB) volume (mm³)	R	30.95	30.00	4.68	33.66	33.00	5.16	0.067
	L	32.91	30.00	5.43	33.22	31.50	5.25	0.398
	p**		0.025			0.776		
Olfactory sulcus (OS) depth (mm)	R	7.73	7.60	1.05	7.27	7.15	0.84	0.287
	L	7.44	7.50	.95908	7.08	7.05	0.99	0.144
	p**		0.228			0.200		
Insular gyrus area (mm²)	R	344.39	340.00	50.36	366.11	375.00	59.50	0.269
	L	363.13	350.00	47.31	363.77	368.00	53.44	0.813
	p**		0.055			0.983		
Corpus amygdala area (mm²)	R	107.78	108.00	16.33	115.50	117.50	20.96	0.184
	L	112.30	111.00	13.24	110.50	105.50	28.42	0.446
	p**		0.055			0.073		

*p-value shows the Mann Whitney U test; **p-value shows the results of Wilcoxon Signed Ranks Test.

Group 2 ($p > 0.05$) (Table 2).

Insular gyrus area

Insular gyrus area values between the two groups were not different ($p > 0.05$). In comparing the right and left sides, insular gyrus area values were not different in Group 1; with the same observation for the control group, Group 2 ($p > 0.05$) (Table 2).

Corpus amygdala area

Corpus amygdala area values of the Groups 1 and 2 were not statistically different ($p > 0.05$). In comparing the right and left sides, corpus amygdala area values were not different in Group 1. The same observation was made for the measurements in Group 2 ($p > 0.05$) (Table 2).

Correlation test results in Group 1 and Group 2 are shown in Table 3:

- For OB volumes, OS depths, insular gyrus areas and corpus amygdala areas, positive correlations were present bilaterally ($p < 0.05$) (Table 3).
- Gender: In females, the right insular gyrus area was significantly lower than that in males ($p < 0.05$) (Table 3).
- B12 levels: In children with lower Vitamin B12 levels, the insular gyrus area on the left and right side gets higher ($p < 0.05$) (Table 3) compared to those with levels within normal limits.
- Hemoglobin: In children with higher hemoglobin levels, the right OB volume gets higher ($p < 0.05$) (Table 3).

- Calcium: In children with lower calcium levels, left corpus amygdala values get higher ($p < 0.05$) (Table 3).

DISCUSSIONS

It is already known that vitamin D3 deficiency is related to many situations involving the central nervous system as it is on many systems. Among these, neuropsychiatric disorders such as multiple sclerosis (MS) and schizophrenia are the best known for their relationship with vitamin D deficiency^{6,7}.

In addition to trauma and infectious conditions in the etiology of odour disorders, many factors such as neurological diseases, metabolic diseases, endocrine diseases, and toxic causes are known to take part¹⁹. It is likely that vitamin D3 deficiency, especially known for its relationship with degeneration and myelin damage, may also affect the olfactory nerve and central odor regions. Although many studies have investigated the relationship between vitamin D deficiency and neuropsychiatric and neurodegenerative disorders, the current study relates to the effects of vitamin D deficiency on the olfactory functions. However, a case report showing that there is a connection between low vitamin D and the sense of smell in two cases encouraged us to do this work¹¹.

As far as we know, our study is the first study that examines

Table 3. Correlation test results in groups 1 and 2*.

			OB Volume (mm ³)		OS Depth (mm)		Insular gyrus area (mm ²)		Corpus amygdala area (mm ²)	
			R	L	R	L	R	L	R	L**
OB volume (mm ³)	R	r		0.685	-0.081	-0.301	0.155	0.126	0.120	-0.074
		P		0.000	0.614	0.056	0.332	0.433	0.456	0.644
	L	r	0.685		0.219	0.047	0.002	-0.048	0.156	0.065
		P	0.000		0.169	0.772	0.991	0.765	0.329	0.688
OS Depth (mm)	R	r	-0.081	0.219		0.763	-0.042	0.081	0.005	0.005
		P	0.614	0.169		0.000	0.797	0.617	0.973	0.977
	L	r	-0.301	0.047	0.763		-0.174	-0.008	0.210	0.159
		P	0.056	0.772	0.000		0.275	0.959	0.188	0.322
Insular gyrus area (mm ²)	R	r	0.155	0.002	-0.042	-0.174		0.531	0.187	0.128
		P	0.332	0.991	0.797	0.275		0.000	0.242	0.425
	L	r	0.126	-0.048	0.081	-0.008	0.531		0.156	0.204
		P	0.433	0.765	0.617	0.959	0.000		0.329	0.202
Corpus amygdala area (mm ²)	R	r	0.120	0.156	0.005	0.210	0.187	0.156		0.714
		P	0.456	0.329	0.973	0.188	0.242	0.329		0.000
	L	r	-0.074	0.065	0.005	0.159	0.128	0.204	0.714	
		P	0.644	0.688	0.977	0.322	0.425	0.202	0.000	
Age	r	0.086	0.280	0.098	0.107	-0.106	0.049	0.025	-0.175	
	P	0.594	0.077	0.543	0.506	0.511	0.759	0.878	0.275	
Gender (Code 1: Male. Code 2: Female)	r	-0.221	-0.103	-0.048	0.066	-0.322	-0.186	0.025	0.122	
	P	0.166	0.523	0.767	0.683	0.040	0.244	0.877	0.446	
25(OH) ₂ D ₃ (ng/mL)	r	0.284	0.181	-0.195	-0.307	0.171	0.154	0.182	-0.049	
	P	0.072	0.258	0.223	0.051	0.286	0.336	0.255	0.760	
Vitamin B12 (pg/ml)	r	-0.162	-0.088	-0.064	-0.178	-0.371	-0.384	-0.073	-0.187	
	p	0.325	0.595	0.700	0.278	0.020	0.016	0.659	0.254	
Hemoglobin (g/dL)	r	0.313	0.265	0.081	-0.052	0.009	0.113	0.020	0.045	
	p	0.049	0.099	0.618	0.749	0.955	0.487	0.902	0.782	
Platelet	r	-0.157	-0.284	-0.110	0.040	-0.251	-0.186	0.016	-0.155	
	p	0.332	0.075	0.498	0.809	0.118	0.252	0.920	0.340	
TSH (μU/mL)	r	0.164	0.145	-0.047	-0.038	0.227	0.124	-0.090	-0.135	
	p	0.368	0.430	0.796	0.835	0.211	0.498	0.624	0.462	
Folic acid (ng/ml)	r	0.235	0.222	0.019	-0.085	-0.091	-0.256	-0.058	-0.157	
	p	0.161	0.186	0.911	0.615	0.593	0.127	0.733	0.352	
Ferritin (μg/L)	r	0.220	0.241	-0.220	-0.111	0.080	-0.137	0.151	0.185	
	p	0.212	0.170	0.212	0.531	0.653	0.439	0.395	0.295	
Calcium (mg/dL)	r	0.323	0.269	0.041	-0.088	0.292	0.014	-0.100	-0.418	
	p	0.082	0.150	0.828	0.645	0.117	0.942	0.599	0.021	
Phosphorus (mg/dL)	r	0.195	-0.060	-0.306	-0.225	-0.188	0.131	-0.315	0.060	
	p	0.452	0.820	0.232	0.385	0.471	0.615	0.218	0.819	

*P-value shows the results of Spearman's correlation rho efficient test; OB: Olfactory bulb. OS: Olfactory sulcus

the relationship between vitamin D deficiency and central odor regions in the childhood age group.

As a result of this work, in the study group with vitamin D3 levels < 20 ng/ml, serum calcium levels were significantly lower than in the control group. This result has been related to the vitamin D levels and their expected effects on Ca metabolism. Hypocalcemia is most commonly caused by vitamin D deficiency²⁰.

In the present study, there were positive correlations between OB volumes, OS depths, and insular gyrus areas, corpus amygdala areas bilaterally. Central smell regions of the insular gyrus and corpus amygdala area were not different between the study group with vitamin D deficiency and the control group. Although there was no difference between the OB volume of the study and control groups, the left OB volume in those with vitamin D deficiency was significantly higher than the right OB volume. This difference between the two sides of OB volumes was not observed in the control group with normal vitamin D levels. Although the right insular area is lower in girls than in males, there is no correlation between OB volume and gender. Higher hemoglobin levels were related to higher OB volume on the right side.

Literature reviews showed that there is a relationship between cerebral lateralization and immune asymmetry^{21,22}. In Dane et al.'s study on young adults, the PPD test was applied to both the right and left arms, showing that the immune system on the left side was more dominant, especially in females²¹. In another study performed by injecting sheep erythrocytes into the paw of the mice, a stronger immune response was observed on the left side²².

When the incidence of autoimmune and inflammatory diseases such as Hashimoto thyroiditis, Crohn's disease, rheumatoid arthritis, ulcerative colitis was compared between the right and left-handed individuals, the incidence rates were higher in the left-handed individuals²⁰. In our patients with vitamin D deficiency, the reason for the asymmetry in the OB volumes may be related to the impaired inflammatory process, which is likely to occur in the individuals with deficiency of vitamin D. This encountered asymmetry should be studied in advanced research.

In the present study, lower vitamin B12 levels were related to a higher insular gyrus area bilaterally; and lower calcium levels were related to higher Corpus amygdala values on the left side. There are two active forms of vitamin B12: methylcobalamin and 5-deoxyadenosyl cobalamin. Methylcobalamin has effects on methionine synthase which helps reactions to make neurotransmitters. Vitamin B12 also helps to make hemoglobin for oxygen transport and maintain healthy myelin. Patients with vitamin B12 deficiency may face a risk of nerve damage due to myelin breakdown²³. In our study, the insular gyrus area was higher in vitamin B12 deficiency. It may be related to the insufficient myelin sheath and probable inflammatory processes due to damaged myelin. These mechanisms should

be investigated in further studies. Our study helped us to notice this issue.

Derin et al. investigated the efficacy of low vitamin B12 levels on olfactory functions²⁴. They applied the Sniffin' Stick test to evaluate the olfactory function. In the vitamin B12-deficient group, the threshold discrimination identification scores were lower than those in the control group. There was a negative correlation between age and odor identification scores. The threshold, discrimination, and identification (TDI) score showed a positive correlation with vitamin B12 levels.

When creating the study and control groups, vitamin D3 levels of the patients were taken into account as low (study group) and normal (control group) as indicated in the method section. The purpose of using other parameters that can be obtained by patients is to not lose sight of and discuss possible situations that may have an impact on the findings obtained as a result of the study. We wanted to draw attention to the fact that there may be additional conditions that are known to have an effect and importance on the neurological system, such as vitamin B12 deficiency, thyroid dysfunction (hypothyroidism, etc.), which can be seen especially with vitamin D3 deficiency (especially in nutritional disorders). Therefore, the relationships we noticed between vitamin B12 level and insular gyrus, but also between calcium level and corpus amygdala measurements were deemed worthy to be shared with the literature and these were included in the discussion section of our article.

CONCLUSIONS

In the group with vitamin D3 deficiency, the olfactory bulb volume on the left side is asymmetrically larger than that on the right side. Therefore, the measurements of vitamin D3 should be performed in adolescents and the patients with the vitamin D3 levels of < 20 ng/ml should be supplemented with medical treatment.

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Authors' information:

Serkan Tursun, Associate Professor, Pediatrics Department, Kırıkkale University, Faculty of Medicine, Kırıkkale, Turkey. E-mail: drtursun@hotmail.com. ORCID: <https://orcid.org/0000-0003-3354-6360>.

Nuray Bayar Muluk, ENT Professor, ENT Department, Kırıkkale University, Faculty of Medicine, Kırıkkale, Turkey. E-mail: nuray.bayar@yahoo.com. ORCID: <https://orcid.org/0000-0003-3602-9289>.

Adnan Özdemir, Associate Professor, Radiology Department, Kırıkkale University, Faculty of Medicine, Kırıkkale, Turkey. E-mail: dradnanozdemir@hotmail.com. ORCID: <https://orcid.org/0000-0003-0652-5396>.

Ziya Şencan, Associate Professor, ENT Department, Kırıkkale University, Faculty of Medicine, Kırıkkale, Turkey. E-mail: drsencan@gmail.com. ORCID: <https://orcid.org/0000-0002-0936-5108>.

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