Golestan University of Medical Sciences
Journal of Clinical and Basic Research
Online ISSN: 2538-3736

Review Article

Investigating Olfactory Bulb Volume Reduction as a Potential Biomarker for Some Neuropsychiatric Disorders: A Narrative Review

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Received August 7, 2021 **Accepted** September 14, 2021

ABSTRACT
The Olfactory bulb is a crucial structure involved in olfaction that is located in the ventral anterior of the forebrain. Due to physiological and anatomical connection between olfactory and emotion processing networks, olfactory dysfunction is seen in some psychiatric disorders. Strong evidences suggest that olfactory bulb volume can mirror olfactory system function. Due to this correlation, there has been an interest to investigate the possible correlation between reduction of olfactory bulb volume and some neuropsychiatric disorders. Nowadays, mental disorders are mostly diagnosed according to behavioural symptoms. Gradual progression of mental disorders and delayed onset of behavioral symptoms have increased the importance of finding objective biomarkers. Such biomarkers can improve treatment outcome, accuracy of diagnosis, and prognosis. It is hypothesized that the reduction of olfactory bulb volume could be a biomarker for some disorders. In this article, we reviewed studies on the association of olfactory bulb volume with depression, Alzheimer's disease, Parkinson's disease, migraine, and multiple sclerosis.

Keywords: Olfactory bulb; Biomarker; Psychiatry; Mental disorder

DOI: 10.29252/Jcbr.5.3.1

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[DOI: 10.52547/jcbr.5.3.9]

Introduction

The olfactory bulb (OB) is a part of the nervous system in the ventral anterior of the forebrain that extends to above the nasal cavity (1). Paired OBs are the first stations in the olfactory pathway that transduce odorant information from olfactory neuron receptors to the primary olfactory cortex i.e. the piriform cortex of the brain (2). This processed information is then transferred to several brain areas, such as the orbitofrontal cortex, amygdala, hypothalamus, insula, ent orhinal cortex, and hippocampus (3). Main OB functions are organized into four groups: odour distinction, enhancing odour detection, removing some background odours, and letting upper brain regions modify detection and discrimination of odours (4). The OB volume is reduced in patients with olfactory disorders (5-9) and may increase during recovery (10). It is hypothesized that this plasticity is because of constant neurogenesis throughout adulthood (11-16). There has been an interest to investigate whether the reduction of OB volume can alert physicians about some neuropsychiatric disorders.

Neuropsychiatric disorder is a term attributed to a broad range of diseases related to both neurology and psychiatry. The World Health Organization (WHO) announced neuropsychiatric disorders as the third most common cause of global disability-adjusted life years worldwide (17) and the leading cause in the USA (18). Some mental disorders, such as depression, can enormously affect the quality of life of individuals. Lack of knowledge about the neurochemical basis of mental disorders is a challenge for physicians to perform pharmacological operations efficiently. On this point, identification of biomarkers is crucial to facilitate prediction and diagnosis of disorders and to operate the therapy procedure at the proper time(19). A Biomarker is defined as an evaluated factor that illustrates normal biological processes, pathological situations, and remedial interferences (20). Nowadays, diagnosing mental disorders with self-reported information and behavioural symptoms is more common than the neural markers. As a result, clinical decision-making relies on the patient's ability to communicate with the physician. The resulting uncertainty and bias will lead to low validity of the physician's diagnose. Therefore, finding neural markers or objective biomarkers may lead us to less bias and more certainty (21, 22). Thanks to the close connection of the olfactory system with emotion regulation networks (23, 24), a number of studies have focused on olfactory disability as such an objective biomarker for different mental disorders (25). The OB volume, which is considered to mirror the functional status of the olfactory system (26-28), is highly under consideration. Here, we review studies that investigated the possible role of OB volume reduction as a biomarker for depression, Alzheimer's disease (AD), Parkinson's disease (PD), migraine, and multiple sclerosis (MS).

MATERIAL AND METHODS

For this purpose, a complete search was done using the following Medical Subject Headings terms: olfactory bulb, depression, neuropsychiatric disease, Alzheimer, Parkinson, MS, migraine, and biomarker in PubMed and Google Scholar. First, 48 original articles were retrieved until July 10, 2021. All articles were imported to Endnote (version X9) and screened by a reviewer. Seven studies were removed by the reviewer because of irrelevancy. Finally, after a deep review of the full-text articles by the main author and removing three more articles due to lack of reliability, 38 original articles were chosen to be reviewed.

RESULTS

Depression

Depression is currently the most prevalent psychiatric disorder. The WHO reported depression as the second cause of disability in 2020 (29). Depression affects 8-12% of the world's population (30). Typical characteristics of major depression are unhappiness, meaninglessness, and irritable mood along with physical and cognitive changes (31). A systematic review has

[DOI: 10.52547/jcbr.5.3.9]

revealed the possible correlation between depression and olfactory dysfunction (32). All the studies used magnetic resonance imaging (MRI) for measurement of OB volume, and some of them reported extra information regarding the olfactory sensitivity, brain grey area, or more statistical analysis

Table 1. Studies investigating OB volume as a biomarker for depression

Study population	Findings of olfactory bulb (OB) volume	Other findings	Reference
21 patients diagnosed with depression and 21 healthy controls	Reduced OB volume in patients (Right: P = 0.025, Left: P = 0.40)	Reduced olfactory sensitivity in patients (P = 0.04)	(33)
24 women diagnosed with depression treated for 10-16 weeks. Respondents (13 patients) and non-respondents (11 patients)	Smaller OB volume in non-respondents (left: p =0.033, Right: p = 0.01).	NA	(34)
32 major depression patients and 51 healthy controls	17% OB volume reduction in patients (58.806±21.39 mm^3) compared to the control group (74.246±17.45 mm^3, p=0.85).	Significant correlation of OB volume with the grey matter volume of areas related to emotion and olfaction such as insula, superior temporal cortex, and amygdala volume.	(35)
84 cases with different mental disorders and 51 healthy volunteers	13.5% reduced OB volume by patients (patients: 64.2±18.5mm^3, healthy controls: 74.2±17.5mm p<0.05).	OB volume reduction reported to be a possible indicator of depression vulnerability by 68.1% accuracy (sensitivity: 71.1%, specificity: 64.4%).	(36)
20 cases with major depression with 3 months of treatment in average and 20 healthy volunteers	No significant difference	NA	(37)
31 patients with chronic major depression and 31 healthy volunteers	Reduced OB volume in patients (right=p<0.01, left=p<0.01).	A negative correlation between Beck's depression inventory depression scores and OB volume (right: r=-0.727 and p<0.01, left: r=-0.717, and p<0.001) was observed.	(38)
30 patients with psychotic disorders (mostly Schizophrenia), 37 patients with anxiety disorder/depression, and 30 controls	The OB volume of both patient groups was markedly lower than the control group (p<0.017).	Olfactory sulcus depth was only lowered notably in patients with anxiety disorder/depression compared to the control group (p<0.017).	(39)

Parkinson's disease

Parkinson's disease is a multifactorial neurodegenerative disease (40). The disease includes disability in some motor functions. As patients age, the motor dysfunction seems to be exacerbated. The symptoms include hypokinesia, bradykinesia, postural instability, rigidity, etc. These symptoms are the results of the changes in the brain, particularly in the substantia nigra pars compacta. Presence of an OB dysfunction in PD patients has been also suggested (41, 42). Loss of smell has been detected in a major group of PD patients that might be caused by neurodegeneration in the OB (43). (Table 2) summarizes the results of studies investigating OB volume reduction as a biomarker for PD. All the following OB volumes have been measured using MRI, and the statistical analyses were done using SPSS.

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[DOI: 10.52547/jcbr.5.3.9]

Table 2. Studies investigating OB volume as a biomarker for PD

Study population	Findings of OB volume	Other findings	Reference
52 IPD patients 31 healthy controls	No significant change was detected. The IPD patients' left and right OB volume was 41.5 mm^3 and 42.1 mm^3, respectively. The right and left OB volume in healthy control subjects was 46.6 mm^3 and 41.0 mm^3, respectively (Right: P=0.10; left: P=0.87	NA	(44)
16 PD patients and 16 healthy participants	The OB volume in PD patients (91.2 ±15.72 mm^3) was significantly less than in the healthy control group (131.4±24.56 mm^3) (P < 0.001).	Alzheimer's disease seems to be correlated with OB volume loss.	(45)
15 PD patients, 15 NPOD patients, and 15 healthy controls	The findings showed that both PD and NPOD patients had decreased OB size compared to the control group (P<0.05).	The results illustrated that the major area of difference between the two sets of patients was mainly observed in the cortical region above the OB.	(46)
20 IPD patients, 14 MSA patients, and 12 healthy controls	Total OB volumes (left and right OB and tract) in IPD patients, MSA patients, and the control group were 55.1±10.7 mm^3, 73.8±9.1 mm^3, and 75.9±8.4 mm^3, respectively. The OB volume of IPD patients was significantly lower than controls and MSA patients (both p-values = 0.000)	The OB volume of MSA patients did not differ from that of controls (p>0.05)	(47)
28 IPD patients and 19 healthy controls	The right and left OB volume in stage 1 IPD participants was 79.30 ± 18.96 mm^3 and 77.80±22.74 mm, respectively. The right and left OB volume in the control group was 68.26±12.47 mm^3 and 70.05±15.82 mm^3, respectively (p=0.018)	NA	(48)
41 IPD patients either TDPD or NTDPD, and 19 healthy participants	The mean right and left OB volumes in the patient group were 40.06±13.45 mm^3 and 38.89±13.71 mm^3, respectively. The mean right and left OB volumes in the control group were 44.05±19.23 mm3 and 41.84±14.76 mm3, respectively (right: p=0.751; left: p=0.611).	Odour identification scores of the right- and left–sided measurements were significantly lower in the patients.	(49)
30 PD patients and 30 non PD healthy controls	The team observed a reduction in OB volume (37.30 ±10.23 mm3, p<0.05)	Reduction in olfactory sulcus depth (8.90±1.42 mm, p<0.05) in PD patients.	(50)
100 IPD patients and 100 healthy controls	The average OB volume was 35.28±5.21 mm in IPD patients and 47.53±6.49 mm in control subjects (p>0.05).	There was no significant difference in the olfactory sulcus depth between the two groups.	(51)

IPD: idiopathic Parkinson's disease; NPOD: non-parkinsonian olfactory dysfunction; MSA: multiple system atrophy; UPSIT: Unified Parkinson's disease rating scale; TDPD: tremor dominant Parkinson's disease; NTDPD: non-tremor dominant Parkinson's disease.

[DOI: 10.52547/jcbr.5.3.9]

Schizophrenia

Schizophrenia is a considerable mental disorder characterized by insanity, insensibility, and cognitive disability, disrupting everyday activities (52). Studies on patients with schizophrenia infer that the brains of these cases have a gross cellular abnormality, but these results have not been authenticated by meticulously controlled investigations, indicating that aggregate brain pathology is not specific to schizophrenia (53). The illness is more common and also severe in males (54). Brain volume varied in patients with both first part and chronic schizophrenia compared with uninfluenced individuals (55).

Nguyen et al. (56) conducted a study to survey the possible OB atrophy and olfactory sulcus depth decrease in schizophrenia patients using MRI. The study included 25 male patients (mean age: 44.25 years) and 25 healthy males (mean age: 41.46 years). The MRI findings showed a major decrease in the right OB volume in cases with schizophrenia compared to the healthy group (t=2.648, DF=1, 48, p=0.011). On the contrary, no significant difference in left OB volume was observed between the two groups (t=1.462, DF=1,48 , p=0.150). Also, they found that people with schizophrenia scored significantly lower on the University of Pennsylvania Smell Identification Test (UPSIT) compared to the healthy group, indicating that the patients' capability to recognize smells correctly is damaged (t=2.680, df=1, 23, p=0.013). They reported that right bulb volume in patients is positively associated with UPSIT points (r=0.574, n=14, p=.032). Overall, these results signify that cases with schizophrenia have olfactory deficiency relative to both mass and function.

In 2000, Turetsky et al. (57) conducted a study on 26 schizophrenia patients (mean age: 37.8 years) and 22 healthy individuals (mean age: 36.6 years). The results of MRI showed that patients had 23% lower bilateral bulb volume compared with the control group (patients: 79.8 mm^3 vs. healthy group: 104.3 mm^3). A positive correlation was also reported between odour threshold sensitivity and OB volume in the healthy group (r=–0.86, N=22, p<0.001), but this association was not observed in the patients (r=0.30, N=26, p=0.14). In another study by Turetsky et al. (58), cases with schizophrenia had a weaker sense of smell compared to the healthy relatives. Olfactory psychophysical gauges and MRI scans of OBs were acquired from 11 patients (mean age: 30.7 years), 19 normal first-degree relatives of patients (mean age: 36.9 years), and 20 healthy control subjects without family history of schizophrenia (mean age: 36.0 years). All the cases underwent MRI, and images were acquired on a 1.5-T GE Signal scanner. A significant difference in left OB volume between the patients and relatives was reported. In addition, major differences in the right OB volume were observed between patients and healthy controls, and between relatives and healthy controls.

Alzheimer's disease

Alzheimer's disease is a chronic neurodegenerative and noticeable protein conformational disease with clear pathophysiological mechanisms (59, 60). The disease generally affects the medial temporal lobe and integrative neocortical system (61). It is one of the most prevalent causes of dementia (62). The OB and OB tract (OBT) atrophies have been reported during AD progression (63).

In 1994, Ter Laak et al. (64) published a study about the relationship between AD and OB. In this study, OB of six people with AD and six healthy cases with the same age and gender were compared. Patients had the same total number of mitral cells compared to the healthy group, but the OB mass and the number of neurons in the anterior olfactory nucleus (AON) was decreased in patients. The loss of AON neurons was only observed in younger cases. Although neurofibrillary tangles (NFT) and senile

[DOI: 10.52547/jcbr.5.3.9]

plaques (SP) were detected in the healthy group, they were more prevalent in patients. Philipp A. Thomann, Dos Santos et al. (65) conducted a study on 21 patients and 21 healthy controls and published some findings. Firstly, in cases with mild AD, the OBT volume was considerably lowered compared to the healthy ones (right: p = 0.001, left: p = 0.003 and mean: p = 0.001). Secondly, in the patient's assembly, the OBT volume was expressively associated with the cognitive function which is determined by the Mini–Mental State Examination (MMSE) (p = 0.004). These data distinctly show us that OBT atrophy is seen in early stages of AD. According to analytical findings, no considerable differences were reported regarding to age, sex distribution, and knowledge.

Thomann et al. (66) revealed a correlation between AD and OBT atrophy using MRI. The mentioned study included 29 patients with mild cognitive impairment, 27 patients with probable AD, and 30 healthy control individuals. The right, left, and mean OBT volume were reported to be highest in healthy cases and lowest in the AD group. In AD cases, voxel-based morphometry showed decreased OBT volumes to be considerably associated with lowered grey matter density in the left-hemispheric amygdala, hippocampus, and parahippocampal gyrus. In AD cases, the OBT volume was significantly associated with MMSE scores (p < 0.01). However, in a study conducted by Servello et al. (67) on 28 healthy cases (22 females and 6 males), 25 patients with MCI (14 females and 11 males), and 25 mild AD patients (14 females and 11 males), there was no apparent difference in the OB volume between the study groups. Moreover, there was no correlation between OB volume and olfactory function.

Multiple sclerosis

Multiple sclerosis is an inflammatory, autoimmune disorder related to the central nervous system. Myelinated axons are attacked in MS, causing gradual neurological deficiency (68). The prevalence of MS varies widely and is higher in the North America and Europe but lower in Eastern Asia (69). Nowadays, studies aim to find MS-specific biomarkers in serum and cerebrospinal fluid (70). We reviewed studies conducted to investigate the possible role of OB volume as a biomarker for MS.

A study by Goektas et al. (71) was conducted to examine the possible correlation of OB volume with olfactory dysfunction in MS patients. Out of 36 MS patients, 44.4% had olfactory dysfunction in the threshold-discrimination-identification exam. Results of MRI showed that nine of 36 patients had OB volumes below the normal level (100 mm^3). In these cases, a strong positive correlation was found between OB volume and olfactory function.

The association of cognitive disability and depression with OB volume in MS patients was investigated in a study by Yaldizl et al. (72). The average OB volume in MS cases was lower than that in the healthy controls (183.9±40.1 vs. 209.2±9.3 µl; p=0.018). This OB atrophy was associated with higher depression scores in MS cases (p<0.05). On the contrary, no significant correlation was reported between reduced OB volume and cognitive impairment.

Migraine

Migraine is an episodic headache that is commonly caused by overexcitability of the central nervous system. The pain caused by migraine is so intolerable that the disease is considered as one the most irritating and debilitating disorders. The illness is diagnosed based on the headache's very own characteristics. In the event of a disabling migraine, the treatment is either triptans or ergots, but if the patient is suffering from high-frequency headaches preventative medications are suggested (73).

Aktürk et al. (74) studied the bilateral changes in the OB, including changes in the OB volume and the olfactory sulcus depth, and their possible correlation to the pain triggered by odours in migraine patients, a situation in migraine patients known as

[DOI: 10.52547/jcbr.5.3.9]

osmophobia. Based on the results, the olfactory sulcus depth did not differ between the migraine patients with or without osmophobia and the healthy control group. In addition, OB volume was significantly lower in migraine patients with or without osmophobia than in the control group (especially in the left OB); however, OB volume was lowest in osmophobic patients. Inconsistent with these findings, Doğan et al. reported that both the OB volume and olfactory sulcus depth decrease significantly in patients with migraine (75).

CONCLUSION

Finding biomarkers (other than behavioral ones) can help diagnosis of mental disorders before symptoms show up. Therefore, disease progression could be prevented, and treatment could be carried out more efficiently. Based on the tight neural connection between the olfactory system and emotion processing, OB volume, as a marker of olfactory function, has received much attention. Based on the studies, it can be concluded that OB volume reduction can be a sign of depression and PD. However, it is not clear whether OB volume reduction can be considered as an independent biomarker for diagnosis of depression and PD. Similar conclusions can be made in case of AD and schizophrenia, but further studies are needed to confirm these conclusions. On the contrary, there is no sufficient evidence for migraine and MS to even consider OB volume reduction as a sign for further examinations. To sum up, we assume that OB volume reduction can be a possible objective biomarker for some psychiatric disorders along with other biomarkers. Although, more studies with larger study populations are essential to declare it with assurance.

ACKNOWLEDGMENTS

None.

DECLARATIONS

Funding

Not applicable.

Ethics approvals and consent to participate

Not applicable.

Conflict of interest

The authors declare that there is no conflict of interest regarding publication of this article.

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How to Cite: Hajishah H, Salehi S A, Amini M. Investigating Olfactory Bulb Volume Reduction as a Potential Biomarker for Some Neuropsychiatric Disorders: A Narrative Review. Journal of Clinical and Basic Research. 2021; 5 (3) :1-12

[DOI: 10.52547/jcbr.5.3.9]