RESEARCH ARTICLE

Reduced olfactory bulb volume in depression—A structural moderator analysis

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Abstract

Background: Removal of the olfactory bulb (OB) leads to depression like behavior in rodents. A link between depression and olfactory function is also established in humans. We hypothesized that the human OB volume relates to depressive state and tested whether such a potential coherence is moderated by structural alterations in other brain regions.

Methods: Eighty-three participants (32 patients with major depression and 51 matched healthy controls) underwent structural MR scanning. Individual OB volumes were compared between patients and controls and the impact of depression and comorbidity was analyzed with multiple regression analysis. Whole-brain voxel-based morphometry revealed structures co-varying with both depressive state and OB volume.

Results: The OB volume of patients was significantly reduced and this reduction averaged out at 17% compared to the controls. The OB volume was correlated to the volume of the insula, superior temporal cortex, and amygdala. The independent variables of depression ($\beta = -.37$), age ($\beta = -.25$), and gender ($\beta = -.40$) explained the individual OB volume variation ($R^2 = .37$). The correlation between OB volume and depression was moderated by volumetric reductions in a cluster including the insula and superior temporal gyrus (STG).

Conclusions: The OB volume relates to depression in humans and to the volume of structures which are critical for salience detection. We assume that a reduced OB volume causes diminished neural olfactory input which facilitates volume reduction in the insula and STG. The OB volume may hence constitute a factor of vulnerability to depression. Olfactory-based deep brain stimulation is discussed as a future therapeutic approach.

KEYWORDS

amygdala, gray matter volume, insula, salience, superior temporal gyrus

1 | INTRODUCTION

Tight functional and anatomical connections exist between olfactory and emotion regulation networks (Gottfried, 2006; LeDoux, 2000). Those connections may explain why mental disorders are often accompanied by abnormalities of olfactory processing (Croy & Hummel, 2016; Kohli, Soler, Nguyen, Muus, & Schlosser, 2016). This affects especially depression, which is linked to reduced olfactory function and to a reduced olfactory bulb (OB) volume (Negoias et al., 2010).

The OB projects directly into the piriform and entorhinal cortex and from there secondary projections reach the amygdala and insula and other secondary and tertiary olfactory structures such as the hippocampus, anterior cingulate cortex, and orbitofrontal cortex (Wilson, Chapuis, & Sullivan, 2015). Therefore, it may be assumed that olfactory processing provides critical neural input into structures which are also known for emotion processing. Of especial interest here are the amygdala and the insula, two neural structures which are not only highly involved in olfaction but also in salience detection and emotion

processing. The amygdala is a limbic structure which is pivotal for aversive learning and accordingly reliably activated following aversive stimuli (Büchel, Morris, Dolan, & Friston, 1998; Rogan, Stäubli, & LeDoux, 1997). The insula, especially its anterior part, is considered as the hub of the salience processing network (Bressler & Menon, 2010), which is critical for the identification of relevant events and for guiding of attention and behavior (Menon, 2015).

The neural function of both regions is moderated by olfactory input, as has been shown in rodents. The rodent insula receives strong projections from olfactory neurons of the piriform cortex (Chen et al., 2014) and efferent fibers from the rodents OB to the amygdala exert a tonic inhibitory control over the amygdaloid activity (Jesberger & Richardson, 1988). It was therefore suggested that disturbance of the olfactory neurocircuit impacts limbic functioning and disrupts emotion processing (Song & Leonard, 2005). In line with this, bilateral removal of the OB in rodents leads to changes in behavior that strikingly parallel human depressive patients (Song & Leonard, 2005) and the disrupted connections between the OB and the olfactory–limbic circuit are supposed to explain this phenomenon (Oral et al., 2013).

The neural connection between olfactory and emotional structures may be less strong in humans (Heimer, Van Hoesen, Trimble, & Zahm, 2007). However, olfaction also mediates human emotion processing. Patients with acquired olfactory disorders have an enhanced vulnerability to depressive symptoms (Croy, Nordin, & Hummel, 2014a; Jung, Lee, & Park, 2014) compared to normosmic controls. Patients with congenital anosmia, a disorder characterized by aplastic OB, report enhanced symptoms of depression (Croy, Negoias, Novakova, Landis, & Hummel, 2012). Furthermore, depressed patients exhibit reduced olfactory functioning (Croy et al., 2014b; Lombion-Pouthier, Vandel, Nezelof, Haffen, & Millot, 2006; Negoias et al., 2010; Pause, Miranda, Goder, Aldenhoff, & Ferstl, 2001). However, some studies found only small, insignificant reductions of olfactory function in depression (for an overview, see Croy & Hummel, 2016; Kohli et al., 2016). The functional link between depression and olfaction is reflected in neural alterations. Depressed patients show prolonged and reduced central neural olfactory processing (Croy et al., 2014b; Pause et al., 2003) and reduced activation of the insula after olfactory stimulation (Croy et al., 2014b). Further, structural MRI investigations revealed a significantly reduced volume of the OB (Negoias et al., 2010) in depression. Thereby, the OB reduction—as well as the reduction of olfactory function—is especially pronounced in those depressive patients with a history of childhood maltreatment (Croy et al., 2013).

Alterations of olfactory function have also been investigated in other mental disorders characterized by emotion regulation deficits, such as schizophrenia, post-traumatic stress disorder, obsessive compulsive, and eating disorder (Atanasova et al., 2008). However, in those disorders, the relation to olfaction is less consistent and—to the best of our knowledge—no studies are published, that examine the structure of the OB in any other mental disorder.

Taken together, the removal of the OB leads to depression-like symptoms in rodents (Song & Leonard, 2005), an aplastic olfactory bulb is related to depressive symptoms in humans (Croy et al., 2012) and depressed patients have a smaller OB than healthy controls (Negoias

et al., 2010). However, the OB as the first central olfactory processing structure is not directly related to depression. We therefore assume that a relation between OB volume and depression is moderated by the volume of other structures implicated in emotion and salience processing. Supporting this assumption, depression is accompanied by reduced gray matter (GM) volume in multiple areas, among others are the amygdala and insula (Bora, Fornito, Pantelis, & Yücel, 2012; Sacher et al., 2012). Those areas also show altered neural functionality in depression (Fitzgerald, Laird, Maller, & Daskalakis, 2008).

The aim of this study was (a) to replicate the relation between human OB volume and depression and (b) to examine neural structures which moderate such a relation. We furthermore investigated whether the relation between OB volume and mental health is exclusive for depression.

2 | METHODS AND MATERIALS

2.1 | Participants

Thirty-two in-patients of the Department of Psychosomatic and Psychotherapy of the Dresden University Hospital were recruited. Those had been previously diagnosed with major depressive disorder by structured anamnestic interviews (Wittchen, 1997) which were performed by trained psychotherapists. The patient group included 17 females and 15 males, aged between 21 and 60 ($M \pm SD = 38.8 \pm 11.9$) years. Further demographic and illness-related parameters are shown in Table 1. The median of the number of overall diagnosed mental disorders was 2 and ranged from 1 to 5 diagnoses. Comorbidities included anxiety disorders ($N = 21$), somatoform disorders ($N = 6$), post-traumatic stress disorder ($N = 12$), substance abuse ($N = 4$), and eating disorders ($N = 6$).

Fifty-one age- and sex-matched healthy controls (26 females and 25 males; 20–69 years; $M \pm SD = 39.16 \pm 12.98$ years) were recruited from a pool of healthy controls and via public announcement on the university campus and they were reimbursed for their participation. Controls were required not to meet criteria of a mental disorder as confirmed by the Patient Health Questionnaire (PHQ; Spitzer, Kroenke, Williams, & Group, 1999). Accordingly, controls exhibited a rather low mean score of 2.74 ($SD = 2.81$, range: 0–12) in the Beck Depression Inventory (BDI; Hautzinger, Keller, & Kühner, 2006). All participants underwent a detailed medical interview and concomitant nasal pathology (severe septum deviation, sinonasal disease), or potential brain pathology served as exclusion criteria for all participants.

The groups did not differ in terms of age ($t(81) = 0.12$, $p = .90$) and sex distribution ($\chi^2(1, 83) = .04$, $p = .85$), but as expected patients reported higher depressive state, more posttraumatic symptoms, more childhood maltreatment and worsened emotion regulation abilities (compare Table 1). Additionally, an unexpected trend for patients ($M \pm SD = 1726.3 \pm 263.5 \text{ mm}^3$) having higher total intracranial volume (TIV) than healthy controls ($M \pm SD = 1628.6 \pm 235.7 \text{ mm}^3$) was observed ($t(81) = 1.76$, $p = .08$) which was one reason to include TIV as control variable in all the analyses.

TABLE 1 Descriptive characteristics of the patient and control group

	Patients (N = 32)		Healthy controls (N = 51)		Comparison
	Mean	SD	Mean	SD	
Age (y)	38.81	11.92	39.16	12.98	$t(83) = 0.12$
OB_left	57.54	17.20	66.96	16.75	$t(83) = 2.47^*$
OB_right	60.37	22.10	71.20	17.07	$t(83) = 2.51^*$
OB_best	58.80	21.39	74.24	17.45	$t(83) = 2.63^*$
Olfactory threshold	9.66	3.42	10.05	3.34	$t(83) = 0.74$
Olfactory identification	26.56	2.33	26.96	2.63	$t(83) = 0.65$
BDI	33.13	11.95	2.75	2.81	$t(83) = 14.14^{***}$
PCL	45.87	22.04	5.14	7.40	$t(83) = 12.13^{***}$
CTQ	60.96	27.29	31.82	5.73	$t(83) = 7.37^{***}$
ERQ_cognitive reappraisal	4.12	1.21	4.93	1.11	$t(83) = 3.06^{**}$
ERQ_expressive suppression	4.67	1.49	3.43	1.16	$t(83) = 4.16^{***}$
Sex	$m = 15$ (46.9%)		$m = 25$ (49%)		$\chi^2(1, 83) = 0.036$
	$f = 17$ (51.8%)		$f = 26$ (51%)		$p = 0.85$
Number of diagnoses	2.64	1.38			
	<i>n</i>	%			

Note. Abbreviations: % = percentage; BDI = score in Beck's Depression Inventory; CTQ = score in Childhood Traumatization Questionnaire; ERQ = score in Emotion Regulation Questionnaire; *n* = number; OB = olfactory bulb; OB_best = greater volume of left or right OB; OB_left = volume of left OB; OB_right = volume of right OB; PCL = score in PTSD Checklist for DSM-5.

Age is displayed in years; volumes of OB are displayed in mm³.

* $p < .05$, ** $p < .01$, *** $p < .001$.

2.2 | Ethics statement

The study followed the Declaration of Helsinki on Biomedical Research Involving Human Subjects and was approved by the local Ethics Committee (EK 51022015). All participants provided written informed consent.

2.3 | Questionnaires

To measure depression severity, we administered the German version of the BDI II (Hautzinger et al., 2006). Childhood maltreatment was measured retrospectively by the German version of the Childhood Traumatization Questionnaire (CTQ; Wingenfeld et al., 2010), post-traumatic symptom severity by the German version of the PTSD Checklist for DSM-5 (PCL; Weathers et al., 2013), and the ability to cope with emotional states by the Emotion Regulation Questionnaire (ERQ; Abler & Kessler, 2009).

2.4 | Olfactory function

Olfactory function was tested using the "Sniffin' Sticks" test battery (Burghart GmbH; compare Bult, de Wijk, & Hummel, 2007) with the subtests of olfactory threshold and the extended version of the odor identification test (Haehner et al., 2009).

2.5 | Magnetic resonance imaging procedures

MRI scans were performed on a 3 T Siemens Magnetom Verio scanner (Siemens Healthcare, Erlangen, Germany) using an 8-channel phased-array

head coil. T1-weighted images were acquired using a 3D magnetization prepared gradient rapid acquisition gradient echo (MPRAGE) sequence, with the following parameters: repetition time (TR) = 2,530 ms; echo time (TE) = 2.34 ms; inversion time (TI) = 1,100 ms; field of view (FOV) = 256 mm; voxel size $1 \times 1 \times 1$ mm³; flip angle 7°, in total 192 contiguous slices of 1 mm thickness. These data were used for subsequent voxel-based morphometry (VBM).

A complementary fast spin-echo T2-weighted sequence covering the anterior and middle segments of the skull base was acquired with the following parameters: TR = 8,090 ms; TE = 97 ms; voxel size $2 \times 2 \times 2$ mm³; flip angle 123°, in total 36 contiguous slices of 2 mm thickness, coronal orientation with no gap. Using these data, OB volume measures were obtained.

2.6 | Statistical analysis

Data were analyzed using SPSS 21 for Windows (SPSS Inc., Chicago, IL, USA). AMIRA 3D visualization and modeling system (Visage Imaging, Carlsbad, USA) was used to calculate OB volumes. VBM analyses were performed with the Cat12 toolbox (<http://dbm.neuro.uni-jena.de/vbm/>) implemented in the SPM12 software (<http://www.fil.ion.ucl.ac.uk/spm/>), which was run under MATLAB (Mathworks, Sherborn, MA, USA).

2.6.1 | Calculation of OB volumes

OB volumes were calculated based on manual segmentation of the acquired T2-weighted coronal data. Left and right OB's limits were

drawn manually on each coronal slice. OB volumes were calculated by planimetric manual contouring (surface in mm^2) and all surfaces were added and multiplied by 2 (2 mm slice thickness) to obtain an estimated overall volume. The pronounced diameter change in transition from bulb to tract was used as the distal demarcation of the OB (compare Figure 1 for a sample MR image of the OB). OB measurements of all participants were performed twice by the same experimenter (FR), blinded to the group category. The results from both measurements were averaged for further statistical analyses. The difference of the two measurements ranged from 0 to 11.2 ($M \pm SD = 4.8 \pm 3.8$) mm^3 .

For reliability purposes, intraclass correlation coefficients for these data were calculated ($ICC = .88$, $p < .001$). A second rater (PH) measured OB volumes of 15 participants for the purpose of calculating the inter-rater correlation ($IRC = .81$, $p < .005$). Consistent with previous studies (Buschhüter et al., 2008), over all participants, the volume of the right OB ($67.02 \pm 19.76 \text{ mm}^3$) was significantly higher than of the left OB ($63.33 \pm 17.44 \text{ mm}^3$, $t = -2.97$, $p < .01$). For each participant, the maximum volume out of the left or right OB was defined as “best OB volume” and used for all further analyses. Hence, the term OB volume refers to “best OB volume.” Previous studies using this approach of calculating and analyzing OB volumes have emphasized its high reliability and accuracy (Mueller et al., 2005; Yousem, Geckle, Doty, & Bilker, 1997).

2.6.2 | Between-group analysis

OB volume was compared between patients and controls using ANCOVA with age, sex and TIV as covariates. Age and sex were chosen as covariate because of decreasing OB volume with age and because of women exhibiting a smaller OB volume than men (Buschhüter et al., 2008). TIV was added as covariate to rule out the effects of different mean TIV in the two groups. Olfactory threshold and odor identification were compared between patients and controls using independent samples t test.

2.6.3 | Multiple regression analysis

Single regression analyses were carried out over all participants to predict the OB volume. The following predictors were chosen: BDI score, psychiatric diagnosis, CTQ score, PCL score, ERQ score, olfactory identification ability, olfactory threshold, sex, age, and TIV. To ensure statistical power, psychiatric diagnoses were grouped into 3 clusters (according to the ICD 10 classification of mental disorders), which were used as independent variables: *affective disorders* [F3] and *neurotic, stress-related and somatoform disorders* [F4]. Further diagnoses (compare Supporting Information, Table 1) occurred in <10 cases and were hence grouped together as *other mental disorders*. The reason for including both, the BDI score as a continuous variable and mood disorders as categorical variable, was that depressive mood, as an accompanying symptom of several mental disorders, could provide additional information.

Significant predictors of OB volume were included in a stepwise forward multiple linear regression analysis to determine which combination of variables predicts OB volume best and to rule out potential interaction effects. For all these analyses, the level of significance was set to $p = .05$.

FIGURE 1 Picture displaying the position of the OB (encircled in yellow) in the human brain [Color figure can be viewed at wileyonlinelibrary.com]

2.6.4 | Voxel-based morphometry

The T1 data were realigned and afterward segmented into GM, white matter (WM), and cerebrospinal fluid (CSF), using the segmentation procedure implemented in SPM. Subsequently, these segmented GM images were spatially normalized to the customized template in standardized anatomic space using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL). Finally, the images were smoothed with a Gaussian kernel (full-width at half-maximum, 8 mm) and normalized to the Montreal Neurological Institute (MNI) space. The individual total TIV was calculated as the sum of the volume of GM, WM, and CSF.

The relation between OB volume and GM volume was analyzed over all participants with a regression design using the OB volume as covariate (for completeness, the separate associations of left respectively right OB with GM volume and the associations of OB- and GM volume in healthy controls are shown in Supporting Information). To avoid possible edge effects between different tissue types, we excluded all voxels with GM values < 0.2 (absolute threshold masking). In the second step, voxel-wise GM differences between depressed patients and controls were compared using independent sample t tests. We confirmed this result by examining the effect of depression severity on regional GM volume over all participants in a regression design. Therefore, the BDI score was used as a covariate over all participants.

To determine areas which were related to both depression and OB volume, a third step was taken. There, we masked the effect of OB volume on GM volume by GM areas which were reduced in patients with depression as compared to controls ($p < .05$, inclusive masking).

The subject's age, sex, and TIV were controlled in all VBM analysis by including them as nuisance effects of no interest in the respective model. A cluster-extent based threshold of $p < .001$ (uncorrected) was considered as statistically significant (Woo, Krishnan, & Wager, 2014) and was used in combination with a nonstationary threshold to balance the risks of Type-I and Type-II errors (Lieberman & Cunningham, 2009). The nonstationary extent threshold was computed with the VBM-8 toolbox for SPM (<http://dbm.neuro.uni-jena.de/vbm>). Significant activations were located with the anatomy toolbox (Eickhoff et al., 2005).

FIGURE 2 Diagram showing the olfactory bulb volumes of each individual of the patient and healthy control group. Olfactory bulb volumes are displayed in mm³. Means of OB volumes for each group are shown in the boxes

Finally, we aimed to access whether OB related GM reduction moderates the relation between olfaction and depression. Therefore, we extracted the GM volume of the area, which was most strongly ($p < .001$) related to both OB volume and depression (patients vs controls). Extraction was performed for each subject using the MarsBaR toolbox (<http://marsbar.sourceforge.net/>; Brett, Anton, Valabregue, & Poline, 2002). A moderation analysis was performed with OB volume as the independent variable, the extracted GM volume as moderator and the severity of depression as dependent variable. A bias-corrected bootstrap method (number of resamples = 10,000) was used as implemented in the SPSS macros of Preacher and Hayes (2008).

3 | RESULTS

3.1 | Reduced OB volume in depression

In line with the hypothesis, a significant effect of group on OB volume was found ($F[2, 83] = 18.70$; $p < .001$; $\eta^2 = .19$). Patients exhibited a 17% smaller OB volume than healthy controls (patients: 58.80 ± 21.39 mm³, healthy controls: 74.24 ± 17.45 mm³, compare Table 1 and Figure 2). Patients also exhibited a slightly reduced olfactory threshold and odor identification compared to healthy controls (compare Table 1 and Supporting Information for further information). However, those differences missed statistical significance.

Single linear regression analyses revealed a significant relation between OB volume and age ($F[1, 81] = 5.93$; $p < .05$; $R^2 = .07$), sex ($F[1, 81] = 17.31$; $p < .001$; $R^2 = .18$), TIV ($F[1, 81] = 3.99$; $p < .05$; $R^2 = 0.05$), severity of depressive symptoms (BDI: $F[1, 81] = 8.85$; $p < .01$; $R^2 = .10$), presence of affective disorders ($F[1, 81] = 12.91$; $p < .01$; $R^2 = .14$) and neurotic, stress-related, and somatoform disorders ($F[1, 81] = 6.76$; $p < .05$; $R^2 = 0.08$). No significant relation was found to the severity of PTSD symptoms (PCL score: $F[1, 79] = 1.96$; $p = .17$), childhood maltreatment (CTQ score: $F[1, 77] = .28$; $p = .60$), emotion regulation (ERQ subscale cognitive reappraisal: $F[1, 78] = .47$;

$p = .49$; subscale expressive suppression ($F[1, 79] = .22$; $p = .64$), other mental disorders ($F[1, 81] = 2.39$; $p = .13$), olfactory identification performance ($F[1, 81] = .199$; $p = .67$) or olfactory threshold ($F[1, 81] = 1.89$; $p = .17$). Hence age, sex, TIV, BDI score, affective disorders and neurotic, stress-related, and somatoform disorders were included in a stepwise forward multiple regression analysis. A significant regression equation was found ($F[3, 79] = 15.34$, $p < .001$; $R^2 = .37$) with sex ($\beta = -.40$; $p < .001$), affective disorders ($\beta = -0.37$; $p < .001$), and age ($\beta = -.25$; $p < .01$) remaining as significant predictors of OB volume.

3.2 | OB volume correlates with the GM volume of emotion eloquent areas

The individual OB volume was positively correlated to GM volume in several emotion and olfactory related brain regions including the bilateral insula cortex, amygdala, hippocampus, gyrus rectus, superior temporal gyrus, and the piriform cortex (for full results, compare Table 2 and Figure 3). No negative correlations were observed.

In the next step, the contrast of OB volume was inclusively masked ($p < .05$) by areas which were reduced in depression (for full results of depression on GM volume, please compare the Supporting Information section). The analysis revealed areas which were related to both, OB volume and depression, namely, the insula lobe, superior temporal gyrus, the inferior frontal gyrus, amygdala, and hippocampus. Importantly, all VBM statistics are corrected for TIV, age, and sex.

3.3 | Relation between OB and depression is moderated by volume of the insula/STG

We further restricted our search to those areas which were most strongly related to depression and OB volume (each $p < .001$). This resulted in one cluster, which included the left insula cortex and extended to the left superior temporal gyrus (peaks at $[-50 \ 2 \ 9]$ and $[-54, -3, 2]$, cluster size = 175 voxels, T score = 3.52, compare Supporting Information, Figure 2). We tested whether the association between OB volume and depression severity was significantly reduced by introducing GM volume of the left insula/STG. In result, the correlation between OB volume and BDI score ($r = -.32$, $p < .005$) diminished when controlled for the left insula/STG GM volume ($r = -.203$, $p = .07$). Hence, the association between OB volume and severity of depression was moderated by the indirect effect of the subcortical GM volume in the left insula/STG (Figure 4).

4 | DISCUSSION

In line with our hypothesis, patients with depression exhibited a reduced OB volume. This reduction of about 17% compared to the OB volume of healthy controls reached a medium effect size. The direction and the amount of OB volume reduction in patients with depression were in agreement to previously published studies (Croy et al., 2013; Negoias et al., 2010) and are also in line with a study showing that another primary olfactory structure, the olfactory sulcus, is significantly reduced in depression (Takahashi et al., 2016). Additionally, inclusion of

TABLE 2 Brain regions with GM volume positive associated with OB volume

Region	Cluster size	Peak <i>T</i>	MNI coordinates			Cluster size after masking ^a
			<i>x</i>	<i>y</i>	<i>z</i>	
Right inferior frontal gyrus extending to insula and putamen	2181	5.45 ^b	51	26	14	1088
		4.62	36	27	5	
		4.61	51	17	15	
Right inferior parietal lobe	328	5.26 ^b	47	−48	38	302
Left superior temporal gyrus, extending to insula	3494	5.09 ^b	−45	−21	47	3470
		5.04 ^b	−48	−9	38	
		4.74	−47	−8	6	
Left insula	626	4.70	−36	26	8	
Left middle temporal gyrus	537	4.27	−48	−57	15	537
		4.13	−54	−56	27	
		4.06	−50	−68	27	
Left middle frontal gyrus	128	4.24	−30	42	30	
Right rectal gyrus including the piriform gyrus and extending to the left orbitofrontal gyrus	497	4.23	14	9	−15	
Right amygdala extending to the hippocampus and parahippocampus	379	4.22	24	−12	−11	347
		3.72	30	−5	−17	
Left rectal gyrus including the piriform gyrus and extending to the left orbitofrontal gyrus	491	4.05	−11	11	−15	365
		3.96	−18	14	−17	
Right superior temporal gyrus extending to middle temporal gyrus	516	3.99	53	−27	5	516
		3.37	56	−23	11	
		3.35	53	−30	−9	
Right inferior frontal gyrus	381	3.99	39	36	32	
		3.59	33	18	53	
		3.53	44	27	44	
Right hippocampus extending to subiculum	319	3.96	24	−35	−12	
		3.69	24	−26	−18	
		3.43	18	−32	−3	
Left inferior temporal	112	3.87	−51	−42	−15	
		3.50	−60	−44	−11	
Right superior temporal gyrus	150	3.72	48	−9	−8	
Left hippocampus	120	3.61	−15	−14	−18	120
		3.28	−24	−18	−12	

Note. Abbreviation: STG = superior temporal gyrus.

Height threshold: $p < .001$ (uncorrected), a nonstationary cluster-extend-based threshold of $k > 139$ voxels was calculated with VBM-8 toolbox for SPM (<http://dbm.neuro.uni-jena.de/vbm>); for reasons of completeness, clusters with $k > 100$ are also reported.

^aThe cluster size is reported after inclusive masking ($p < .05$) with areas reduced in the patients vs controls contrast; areas which are significant after masking are highlighted in bold.

^bVolume reductions which hold for a whole-brain peak family wise error (FWE) correction ($p < .05$) are highlighted.

mental comorbidity as covariate in a multivariate regression model revealed that only the diagnosis of depression related to OB volume, while other mental disorders failed significance. The composition of our patients group, which involved a limited spectrum of mental disorders apart from depression, limits the generality of this result. Hence, further studies with larger sample size are required and currently conducted in our group.

The OB volume was positively correlated to other structures of the olfactory network, such as the insula, amygdala, hippocampus, orbitofrontal cortex, and gyrus rectus, and furthermore, the correlation expanded to the STG. The observed relations are in coherence with a previously published study which was conducted in patients with chronic rhinosinusitis and healthy controls (Han et al., 2017). Interestingly, gray matter of insula and orbitofrontal cortex is—among other

FIGURE 3 Brain maps showing positive association between gray matter volume and olfactory bulb volume (upper panel), areas with reduced GM volume in depression (mid panel), and the positive association between gray matter volume and OB volume after inclusive masking for areas that are reduced in depression (lower panel). All brain maps are thresholded at $p < .001$ with a non-stationary cluster-extent-based threshold of $k > 139$ voxels which was calculated with VBM-8 toolbox for SPM (<http://dbm.neuro.uni-jena.de/vbm>). The data are visualized on a template provided by MRIcron (www.nitrc.org/projects/mricron) [Color figure can be viewed at wileyonlinelibrary.com]

areas as ACC, piriform cortex, and cerebellum—found to decrease after olfactory loss (Reichert & Schöpf, 2017). Especially, the correlations of OB volume to the insula, STG, and amygdala are of further interest as those structures are pivotal for salience detection and emotion processing (Bressler & Menon, 2010; Büchel et al., 1998; Downar, Crawley,

Mikulis, & Davis, 2002; Menon, 2015; Rogan et al., 1997) and are assumed to play a major role in the psychopathology of depression (Fitzgerald et al., 2008; Grieve, Korgaonkar, Koslow, Gordon, & Williams, 2013; Kempton et al., 2011). Those structures were still significantly related to the OB after including depression as a masking contrast. Hence, those volumetric GM reductions in those areas were related to both depression and reduced OB volume.

One cluster, involving the left STG and the lateral insula, was most strongly related to depression and OB volume and the moderator analysis revealed that the association between depression and OB volume was moderated by this cluster. The majority of the cluster was assigned to the STG, a region of the temporo-parietal junction which is involved in salience processing of novel stimuli (Downar et al., 2002) and in social cognition (Allison, Puce, & McCarthy, 2000). STG volume reductions have previously been identified in mental disorders like depression (Takahashi et al., 2009), bipolar disorder (Chen et al., 2004; Takahashi et al., 2010), schizophrenia (Takahashi et al., 2009), and psychopathy (Müller et al., 2008). The insula is also involved in salience detection and Menon and Uddin (2010) conceptualize two of the main functions of the insula as detection of salient events inside and outside the own body and modulation of autonomic reactivity to salient stimuli. Increasing research suggests that depressed symptoms may arise from a disturbed integration of intero- and exteroceptive stimuli (Harshaw, 2015), caused by maladaptive changes within the salience network (Menon, 2011). This could lead to the observed bias toward internal thoughts at the cost of engaging with the external world in depression (Kaiser, Andrews-Hanna, Wager, & Pizzagalli, 2015). The association of reduced olfactory functioning as an exteroceptive sensory system,

FIGURE 4 Association between OB volume and severity of depression (BDI score) was moderated by the GM volume in the left STG/insula. Path a illustrates the association between OB volume and GM volume in the left STG/insula; Path b indicates the association between depression severity (BDI score) and GM volume in the left STG/insula; Path c illustrates the indirect association between OB volume and depression score (BDI) (in black); Path c' illustrates the direct association between OB volume and depression severity (BDI score) after controlling for GM volume of the left STG/insula (in red). Correlations and levels of significance are shown next to arrows. All analyses were controlled for TIV

reduced OB volume, and depression may hence be explained by disrupted salience processing.

There are two major limitations in interpreting this study. One concerns the relation between structural and functional data. We only examined structural data and reduced volume may not directly transfer to reduced function. However for the OB it has been shown, that reduced volume relates to reduced olfactory function (Buschhüter et al., 2008; Negoias et al., 2010) and in depression, regions with diminished volume often exhibit reduced functionality (Fitzgerald et al., 2008). Importantly, this is the case for the insula and STG, where both reduced function (Fitzgerald et al., 2008; Liu et al., 2010) and structure (Bora et al., 2012; Takahashi et al., 2010; van Tol et al., 2010) have been observed in depression. The second limitation concerns the cross-sectional character of the study, which makes it impossible to detect causal relationships. However, our results allow the discussion of three possible explanations of the neural mechanisms which drive the association of OB volume with depression.

The first explanation relates to disrupted neuroplasticity in depression (Pittenger & Duman, 2008). The elevated release of biochemical stress molecules as inflammatory cytokines during depression (Furtado & Katzman, 2015) has been shown to limit hippocampal neurogenesis (Sahay & Hen, 2007). The same mechanism could apply for OB volume reduction by limiting the proliferation of central and peripheral olfactory neurons (Yuan & Slotnick, 2014). However, other more specific mechanisms are possible as well.

A second explanatory model states, that the diminished volume of the identified cluster causes both, the reduction of the OB volume as well as depression. A reduced volume of STG and insula may lead to reduced engagement with the external environment and may also—if happening for a long period of time—reduce synaptic connectivity within the olfactory bulb volume (Croy & Hummel, 2016). As insula functioning recovers with remission of depression (Wiebking et al., 2015), OB volume would be expected to also recover after remission of depression. However, although the OB has the potential for volume increase (Gudziol et al., 2009; Negoias, Pietsch, & Hummel, 2016b), the OB volume of depressed individuals does not increase after successful antidepressive therapy (Negoias et al., 2016a). This does not support the hypothesis that the reduction of the identified cluster causes both depression and OB volume reduction.

We are therefore in favor of a third possible explanation and assume that the reduced OB is a factor of vulnerability for depression. Reduced OB volume may lead to reduced neural (olfactory) input to the subsequent structures including the amygdala, insula, and later on STG and orbitofrontal cortex. This reduced input may then reduce synaptogenesis in the subsequent structures and result in the observed correlation between volume of OB and a variety of olfactory relevant structures, including the insula and STG. Decreased volume of the latter structures may impact the detection of salient environmental stimuli. In a vicious circle, the impaired salience detection could then reinforce reduced synaptogenesis at the OB. Such a twofold mechanism of olfaction and depression has already been introduced before (Croy & Hummel, 2016). Therefore, reduced OB volume may serve as a biological marker for depression. However, large-scale studies providing data of sensitivity and specificity are required to explore this possibility.

Furthermore, our study supports the idea of an olfactory-based antidepressive treatment. The OB constitutes a minimally invasive entryway into the brain. A recent study showed that electrical olfactory nerve stimulation activates the OB and alters the resting-state connectivity of the piriform cortex to thalamus, putamen, and insula (Weiss et al., 2016). In the future, deep brain stimulation targeting the salience processing network may be performed via the olfactory nerve to enhance general attentiveness.

In conclusion, the OB volume relates to depression and this relation is moderated by the volume of a cluster including the insula and the STG which are both pivotal in salience processing. We discussed different explanatory models and came to the assumption that the OB provides critical input into structures relevant for salience detection and may constitute a factor of vulnerability to depression.

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