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ORIGINAL RESEARCH

Olfactory bulb volume predicts therapeutic outcome in major depression disorder

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Abstract The volume of the olfactory bulb (OB) is strongly reduced in patients with major depressive disorder (MDD) and this group exhibits markedly decreased olfactory function. It has been suggested that olfactory input is important for maintaining balance in limbic neurocircuits. The aim of our study was to investigate whether reduced OB volume is associated with response to therapy in MDD. Twenty-four inpatients (all women, age 21–49 years, mean 38±10 years SD) with MDD and 36 healthy controls (all women, age 20–52 years, mean 36±10 years SD) underwent structural MRI. OB volume was compared between responders (N=13) and non-responders (N=11) to psychotherapy. Retest of OB volume was performed about 6 months after the end of therapy in nine of the patients. Therapy responders exhibited no significant difference in OB volume compared to healthy controls. However, average OB volume of non-responders was 23 % smaller compared to responders (p=.0011). Furthermore, OB volume was correlated with the change of depression severity (r=.46, p=.024). Volume of the OB did not change in the course of therapy. OB volume may be a biological vulnerability factor for the occurrence and/or maintenance of depression, at least in women.

Keywords Olfactory bulb · Olfaction · Depression · Therapy outcome

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Background

Patients with acute major depressive disorder (MDD) exhibit a significantly reduced volume of the olfactory bulb (OB) (Negoias et al. 2010). The OB is the first central relay station of olfactory processing and its volume is highly correlated to olfactory function (Buschhuter et al. 2008; Hummel et al. 2013a; Yousem et al. 1996). Consequently, MDD is accompanied by the decline of primary and secondary olfactory processing ((Croy et al. 2014b) and review in (Schablitzky and Pause 2014)). When following up those results we found that people with a history of childhood maltreatment form a subgroup of patients with depression that is characterized by further reduction of the OB volume and olfactory sensitivity (Croy et al. 2013). We therefore assumed that severe traumatic stress in childhood leads to a reduction of OB volume, possibly by mechanisms of reduced neurogenesis in early childhood. We further hypothesized that a reduced OB volume would be associated with the risk for imbalance of emotion processing.

Diminished olfactory input to the limbic system may explain the observed relation between depression and olfactory structure and function. The strong connection between OB and depression has been shown a decade ago in rodents and since the bulbectomised rat has been used as an animal model for depression (Song and Leonard 2005). The human OB has strong projections into amygdaloid nuclei and further on into hippocampus, anterior cingulate cortex, insular regions and

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orbitofrontal cortex (Gottfried 2006), all known to be involved in emotion processing. Likewise, reward areas are reliably activated following olfactory input (Gottfried et al. 2003; Lundstrom et al. 2013; Rolls et al. 2010). A reduction of olfactory input could have potential consequences for the balance of neuronal emotion processing and thereby make people more vulnerable to depression.

Alternatively, alterations of olfactory structure and function may be a temporal phenomenon following depression and disappear after remission of the disease. Supporting this notion, secondary olfactory processing shows improvement through the course of therapy ((Croy et al. 2014b; Pause et al. 2003)). For olfactory structures, changes in the course of therapy have not been examined yet. If the connection between depression and olfaction is a temporal phenomenon that disappears after remission of depression, OB volume could also be hypothesized to recover after successful psychotherapy. Volumetric changes of the OB are described in several studies in humans both in connection to peripheral ((Gudziol et al. 2009; Haehner et al. 2008)) or central disorders (Hummel et al. 2013b; Turetsky et al. 2000, 2003; Yousem et al. 1998, 1999). However, studies provide contradictory information on the potential for neurogenesis either within the OB or through progenitor cells derived from the sub-ventricular zone (SVZ) through the rostral migratory stream (RMS) (see (Bergmann et al. 2012; Huart et al. 2013; Lotsch et al. 2013) for ongoing debate).

We assume that a small OB volume is a factor of vulnerability that renders people more susceptible for the maintenance of depression and in consequence hinders therapeutic success. Testing a series of patients initially hospitalized for acute MDD, we were able to study whether a small OB volume is a predictor of poor psychotherapeutic outcome and whether the OB volume is stable in the course of psychotherapy.

Methods

Participants and procedure

A total of 24 women (age 21–49 years, mean 37.8±9.6 years SD) treated in the Clinic of Psychotherapy and Psychosomatic Medicine of the University Hospital Dresden was included in the study. The sample was limited to women because men and women have been shown to differ in olfactory function (Doty and Cameron 2009) as well as in OB volume (Buschhuter et al. 2008) and we decided to exclude sex as a potential source of variance. As there are more women than men treated in the clinic where patients were recruited, women were chosen for pragmatic reasons. All participants were treated for acute major depressive disorder as the leading diagnosis (F32 and F33, ICD-10) and underwent a cycle of inpatient psychotherapy for 10 to 16 weeks (mean 86.2±13.6 days SD). Detailed structured interviews were performed by trained psychotherapists to confirm the diagnosis. Depression level at the time of the examination and at the end of therapy was assessed using the German version of Beck's Depression Inventory (BDI) (Beck et al. 1996; Hautzinger et al. 1995). Additional diagnostic and demographic data are included in Table 1 and supplementary Table S1. Shortly before onset of therapy, all patients underwent a series of examinations: Detailed medical history review and ENT examination were performed to exclude sources of olfactory disorders; mini mental state examination (MMSE (Folstein et al. 1975) was employed to screen for possible cognitive impairment; olfactory function was tested using the "Sniffin' Sticks" test battery (Burghart GmbH, Wedel, Germany; compare (Hummel et al. 2007)).

Therapeutic success for each patient was defined based on the BDI scores before and at the end of the inpatient treatment. A "clinical change index" with a cutoff of 95 % security (single tailed) was calculated (Jacobson and Truax 1991). The advantage of this index is that it takes the initial BDI score in addition to the BDI difference into account in order to estimate a meaningful clinical change. Two groups emerged: patients with positive response to therapy ("responders", 13 patients) and with refractory response to therapy ("non-responders", 11 patients). The groups did not differ in terms of age, diagnosis or BDI scores before therapy. BDI scores after therapy differed significantly (p=0.004; see Table 1).

Nine patients were recalled for a second identical set of examinations about 8 months after therapy (mean age 35.2± 10.9 years, mean time between examinations 247±65 days). This delay was chosen in order to stabilize remission and to give the olfactory system ample time for recovery (Gudziol et al. 2009; Haehner et al. 2008). Seven of the patients were diagnosed with recurrent depressive disorder (ICD 10: F33) and two with depressive episode (ICD 10: F32). Six of the patients were responders to therapy (five with recurrent episodes, one with first episode) while three did not respond (two with recurrent episodes, one with first episode). The change in the BDI score between the two sessions missed statistical significance (p=0.08). Compared to patients without recall, there were no significant differences in symptom severity before or after therapy.

Healthy control group

A second group of participants was included for visualization of OB volume in healthy controls. This sample consisted of 36 female participants, initially enrolled in two other studies. Participants' age was 20–52 years (mean 36.2±10.1 years SD) and did not differ compared to the group of patients (p=0.6). All participants were tested for olfactory function with the extended version of the "Sniffin' Sticks"

Table 1 Demographic data including BDI score before and after inpatient therapy for acute MDD as well as olfactory function and OB volume for therapy responders and non-responders as measured before therapy begin

		Patients					Healthy participants	
		Non responders		Responders				
		N=11		*N*=13		t-test	*N*=36	
		Mean	SD	Mean	SD		Mean	SD
Descriptive information	Age	35.9	9.7	39.3	9.5	n.s	32.4	8.2
	BDI before therapy	31.5	13.8	31.6	9.5	n.s		
	BDI after therapy	34.3	13.8	17.1	12.7	0.004		
Initial odor processing	Threshold	7.7	4.1	8.2	2.4	n.s		
	Discrimination	12.2	1.8	13.2	2.2	n.s		
	Identification	13.4	1.9	13.8	1.4	n.s	14.0	1.1
Initial OB volume	OB volume right	45.6	4.6	57.8	9.8	0.001	58.1	12.3
	OB volume left	47.5	9.8	57.9	12.3	0.033	57.6	11.1
	OB volume highest	49.3	8.9	60.6	10.7	0.011	60.5	12.0
	OB volume mean	46.5	6.6	57.8	10.5	0.005	57.9	11.3

Data of a group of healthy participants is presented for visualization purpose. *Ns*… not significant

identification test (Haehner et al. 2009) at the first appointment. Scores of the extended version were transformed to scores of the normal version (division by two) in order to allow comparability with the sample of patients. All of the healthy participants exhibited normal olfactory function (corrected identification score≥11). All participants received an OB volume scanning session and 14 of them were recalled after 47 to 252 days (mean 154±80 days SD) for a second MRI scanning and retest of olfactory identification. As the participants were initially recruited for other studies, no depression measurements were taken. However, only participants with perfect subjective health, assured by detailed medical history, had been included.

MRI protocol

MRI measurements were performed with a 1.5-Tesla scanner (Sonata Vision; Siemens, Erlangen, Germany) using an eight channel-head coil. The protocol included a whole brain anatomical sequence without interslice gap (5-mm-thick standard T1-weighted 3D sequence) for every participant to rule out any organic brain disorders. The OB sequence included acquisition of 2-mm-thick T2-weighted fast spin-echo images, with 2 by 2 mm voxel dimension, without interslice gap in the coronal plane covering the anterior and middle segments of the base of the skull. Images were offline processed and left and right OBs limits were drawn manually on each coronal slice using the AMIRA 3D visualization and modeling system (Visage Imaging, Carlsbad, USA). 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 a volume in cubic millimeters. The sudden change of diameter at the beginning of the olfactory tract was used as the distal demarcation of the OB, as suggested by Yousem et al. (1997, 1998). The described procedure was used in multiple studies focusing on OB volumetrics, with consistent results, e.g. (Buschhuter et al. 2008; Croy et al. 2013; Hummel et al. 2013a; Negoias et al. 2010).

OB measurements of all data—patients and healthy group members —were performed by the same experimenter (SN) who was blind to the group category of patients and to their respective olfactory test results. It cannot totally be excluded that the experimenter was influenced by the results of the patients' study, when scoring the healthy group. However, the healthy group was initially enrolled and scored for independent studies, which is supposed to minimize expectation effects on the experimenter's side.

Left, right, and mean OB volumes, as well as the highest (best) OB volume, were used for further analyses. Previous research suggest, that overall olfactory function is determined by performance values for the best nostril (Betchen and Doty 1998; Frasnelli et al. 2002) and that the OB volume is higher on the side corresponding to the best nostril (Hummel et al. 2013a). Therefore the highest OB volume can be assumed to determine overall olfactory function.

Statistical analysis

Data were analyzed using SPSS 20 (SPSS Inc., Chicago, Ill, USA). OB volume of therapy responders, non-responders and healthy controls was compared using a multivariate ANOVA with the factors left and right OB volume. Post-hoc tests on

the right, left, mean, and best OB were performed with t-tests for independent samples.

The groups of therapy responders and non-responders were compared for odor threshold, identification, and discrimination scores with t-tests for independent samples. The correlation between the initial OB volume and the change of BDI scores in the course of psychotherapy was calculated according to Pearson.

OB volumes before and after therapy were compared with the use of the distribution free Mann–Whitney-U-test and Spearman correlation coefficients, due to the relatively small sample size. Furthermore OB volume of both measurements in controls was investigated in the same way. Alpha level was set at 0.05, two-tailed.

Results

Initial OB volume is related to therapy outcome

No significant differences were found in terms of olfactory threshold, odor discrimination, and odor identification abilities between the two groups of patients and no significant differences were found in olfactory identification between patients and controls. Average olfactory function of the therapeutic responders was on the 50th percentile in relation to an age and gender corrected sample (Hummel et al. 2007), while therapeutic non-responders performed at the level short above the 25th percentile. Healthy participants performed at the level of the 50th percentile.

The initial OB volume varied between therapy responders, non-responders, and healthy controls ($F[52,2]=2.8$, $p=0.03$). Post hoc testing revealed that non-responders exhibited smaller OB volume compared to responders. This was true for the right ($t[22]=3.8$, $p=0.001$) and left ($t[22]=2.3$, $p=0.033$) OB, and accordingly for the combined measurements of the mean OB volume ($t[22]=3.1$, $p=0.005$) and best OB volume ($t[22]=2.8$, $p=0.011$). Furthermore, non-responders exhibited smaller OB volumes compared to healthy controls (right: $t[40]=4.8$, $p<0.001$; left: $t[40]=2.7$, $p=0.011$; mean: $t[40]=3.2$, $p=0.003$; best: $t[40]=2.8$, $p=0.007$). There was no significant difference between therapy responders and healthy controls.

There was a significant correlation between the initially best OB volume and the change of BDI scores in the course of therapy ($r[24]=.46$, $p=0.024$).

OB volume does not change in the course of therapy

For patients, no significant differences in OB volume were found between the two sessions (compare Table 2) and OB volume before and after therapy was highly correlated ($r=0.94$, $p<0.001$, compare Figs. 1 and 2). In the 14 healthy participants as well, the OB volume was found to be stable over the two measurements ($r[14]=0.94$, $p<0.001$).

Table 2 Results of OB volumes (mm^3) and olfactory function before (session 1) and after inpatient psychotherapy (session 2)

	Session	N	Mean	SD	*p*-value (Mann-Witney test)
OB volume right	1	9	53.61	13.14	n.s.
	2	9	52.73	12.16	
OB volume left	1	9	52.09	15.21	n.s.
	2	9	50.57	13.58	
OB volume highest	1	9	55.20	13.62	n.s.
	2	9	53.79	11.87	
OB volume mean	1	9	52.85	13.89	n.s.
	2	9	51.65	12.59	

Discussion

In accordance with our hypothesis, we found that initial volume of the OB was related to remission of depression. Patients with significant improvement in depressive symptoms had OB volumes that were similar to those of healthy controls, while non-responders exhibited significantly smaller OB volume. The average difference between responders and non-responders was 23 % and OB size was strongly associated

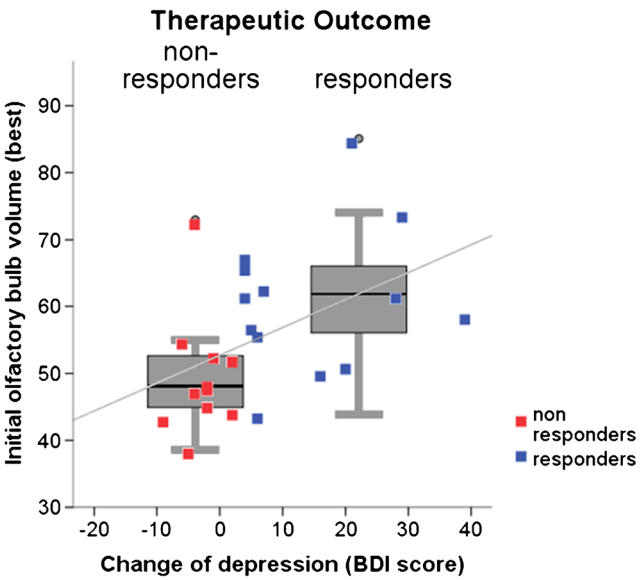

Fig. 1 Olfactory bulb volume in relation to therapeutic outcome. The Figure shows the individual data of the initial OB volume in mm^3 in relation to the change of depression (BDI score after – before therapy). This is superimposed on the box plot of non-responders and responders. *Grey circles above the boxplot* represent individual outliers. The responders exhibited a significantly enhanced OB volume and for the individual data a significant correlation between the initial OB volume and the change of depression was found

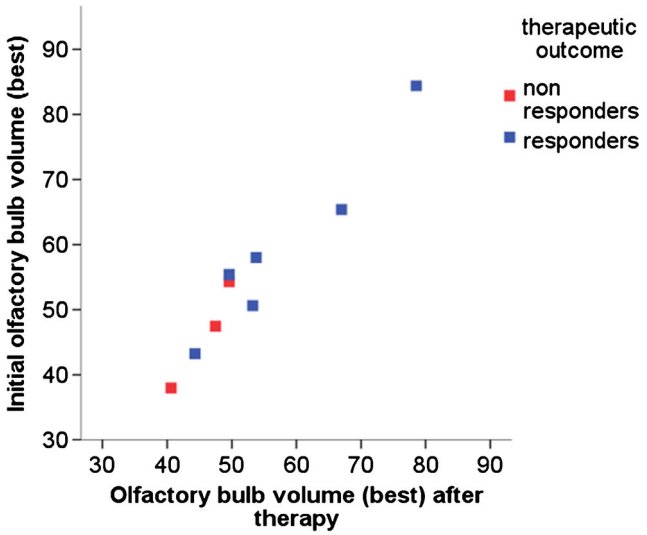

Fig. 2 Olfactory bulb volume before and after therapy

with the improvement of the BDI score. Importantly, responders and non-responders were similar in terms of BDI scores before therapy.

However, it has to be mentioned, that the control group was not initially enrolled in the study and though scoring was blinded between the groups of patients, it was not between patients and controls. There are several other limitations in the study that make us cautious in interpretation. Patients were grouped based on their therapeutic outcome and in consequence the categories of therapeutic responders vs non-responders were built retrospectively. Yet, using an explorative prospective approach - splitting the whole group of patients by the mean of the initial OB volume—we found as well higher improvement in the BDI dependent clinical change score in those with the higher OB volume (p=0.056). Further, therapeutic outcome was measured by subjective BDI ratings, because it reflects the patient's subjective emotional depression state. Other measurements of improvement, such as enhanced structure in daily life and mobilization—would be possible. However, the subjective emotional experience is in our opinion well reflected by BDI ratings. Another critique may refer to the fact that we included women only. Whether the results can be replicated in men needs to be established in further studies.

We proposed two alternative pathways for the known relation between depression and olfaction. Hypothesis one stated that a reduced olfactory input is a factor that renders people more vulnerable to the development and/or maintenance of depressive disorders. The alternative hypothesis stated that reduced olfactory structure is a temporal phenomenon in depression that disappears after remission.

Overall, we are in favor of hypothesis one. The observed smaller OB volume in non-responders may lead to diminished olfactory input in neural emotion processing structures and thus bear a risk for deficits in emotion processing and enhance vulnerability for depression. Conversely, smaller OBs in non-responders were not reflected by reduced olfactory function in our study. Although non-responders scored low on tests of olfactory function compared to responders this effect missed statistical significance; more data is warranted here. The relation between therapeutic response and OB volume may as well be moderated by another underlying variable, e.g., non-responders may possess pervasive limbic system abnormalities that affect OB volume.

As the OB volume did not change within 6 months after the course of therapy, neither in the three non-responders nor in the six responders, reduced OB volume does not seem to be a temporal phenomenon. However, this may be different for olfactory function: while some authors describe an increase of olfactory sensitivity during remission of depression (Pause et al. 2003), we find olfactory sensitivity to remain relatively stable (Croy et al. 2014b). In contrast and consistent with previous findings (Pause et al. 2003) improvement in olfactory identification, improvements in neural responses in the late ERP components and enhanced activation in secondary olfactory areas have been previously observed in the course of therapy (Croy et al. 2014b).

It is interesting to note, that the relation between depression and olfaction is reciprocal. About one third of people who lost their sense of smell (and call at a specialized Smell & Taste Clinic) report symptoms that are in the range of a mild depression (Croy et al. 2014a). Importantly, this is not fully explained by coping problems after loss of a function. People who were born without a sense of smell show a similar enhanced likelihood of depressive symptomatology (Croy et al. 2012).

We conclude that the OB volume is related to depression and may be a promising marker for therapeutic outcome in MDD.

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Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. The study was approved by the Ethics Committee from the Technical University of the Dresden Medical School (EK254102008). Informed consent was obtained from all patients for being included in the study.

Conflict of interest Simona Negoias, Thomas Hummel, Anja Symmank, Julia Schellong, Peter Joraschky, and Ilona Croy declare that they have no conflicts of interest.

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