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# Reduced Olfactory Bulb Volume in Adults with a History of Childhood Maltreatment

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## Abstract

The human olfactory bulb (OB) is the first relay station of the olfactory pathway and may have the potential for postnatal neurogenesis in early childhood. In animals, chronic stress affects the OB and olfactory functioning. For humans, it has been shown that major depressive disorder is accompanied by reduced OB volume and reduced olfactory function. However, it is not clear if major stress in childhood development also affects olfactory functioning and OB volume in humans. OB volume was measured and olfactory function was tested in 17 depressive patients with and 10 without a history of severe childhood maltreatment (CM). CM patients exhibited a significantly reduced olfactory threshold and identification ability. The OB volume of the CM patients was significantly reduced to 80% of the non-CM patients. In conclusion, postnatal neurogenesis might be by reduced in CM, which may affect olfactory function of the brain in later life. Alternatively, a reduced OB volume may enhance psychological vulnerability in the presence of adverse childhood conditions although other areas not analyzed in this study may also be involved.

**Key words:** childhood maltreatment, child abuse, depression, olfaction, olfactory bulb, olfactory threshold

## Introduction

The olfactory bulb (OB) is the first relay station of the olfactory pathway and a highly plastic structure. The volume of the OB correlates with individual differences in olfactory function (Yousem et al. 1999; Buschhuter et al. 2009; Hummel et al. 2011). Interestingly, reduced olfactory function in patients with major depressive disorder is also reflected by reduced OB volume (Negoias et al. 2010).

The OB attracts special attention because it is one of the few brain regions where postnatal neuroplasticity has been shown (Altman 1969). It has been revealed in animal studies that the OB volume decreases after sensory deprivation and increases again after normal stimulation (Cummings et al. 1997). The explanatory model is that subventricular cells reach the OB via the rostral migration stream and add new neurons to the OB (Curtis et al. 2007). However, it is a matter of discussion whether the adult human subventricular zone has the potential for neurogenesis (Rakic 2002; Breunig et al. 2007; Curtis et al. 2007; Pignatelli and Belluzzi 2011). Bergmann et al. (2012) for instance measured the age of human olfactory neurons and argued that there is "very limited, if any, postnatal neurogenesis in the human olfactory bulb" (Bergmann et al. 2012). In contrast, Sanai et al. (2011) used another method for examining the histological material from children and concluded that the corridor of migrating immature neurons is wide in early childhood. According to their model, in this first time of neurogenesis, some of the neurons from the rostral migration stream and subventricular zone are destined for the OB. However, a major pathway also leads to the prefrontal cortex (Sanai et al. 2011). Animal studies suggest that chronic stress affects neurogenesis of neural stem cells in the subventricular zone (Hitoshi et al. 2007). It is not known whether OB volume in humans is affected by major disturbances during the

sensitive childhood development. If so, this could indicate affected neurogenesis.

Childhood maltreatment (CM) is one of the most prominent stressors in human development and is connected to increased inflammatory proteins (Frodl et al. 2012), reduced volume of parts of the hippocampus (Teicher et al. 2012), and reduced medial prefrontal cortex volume (van Harmelen et al. 2010) in adulthood. Borderline personality disorder, a disorder characterized by enhanced and often perilous impulsive behavior, is enhanced by a factor of 7.7 in people who experienced severe childhood abuse (Johnson et al. 1999).

We aimed to study whether adults with a history of CM exhibit reduced OB volume. It has been shown that the OB volume is reduced in patients with major depression (Negoias et al. 2010). In order to overcome a commixture between CM and depression, a group of psychosomatic inpatients is analyzed with similar depression severity.

## Materials and methods

### Participants

A total of 27 women participated. All women were in-patients at the Clinic of Psychosomatic and Psychotherapy of the University Hospital Dresden. Two groups of patients were asked to participate: Women with a history of severe CM and women without major disturbances in childhood development. Participants were preselected by detailed anamnestic interviews, which were performed by trained psychotherapists of the Clinic of Psychosomatic and Psychotherapy. Those patients filled out the childhood trauma questionnaire (CTQ, Bernstein et al. 1997), designed to retrospectively assess 5 types of adverse childhood experiences. Criterion was that the CM patients reported at least an average score of 11 in the CTQ, indicating the 95th percentile in the normative sample (Scher et al. 2001). Participants reporting CM in the anamnestic interview but not in the questionnaire, or vice versa, were not included in the study.

In order to control for random effects of olfactory disorders, for example caused by sinunasal diseases or head trauma, only participants with an olfactory threshold in of at least 4 in the Sniffin' Sticks test (Hummel et al. 1997) were included. This cut-off resembles the 10th percentile of the normative female population (Hummel et al. 2007). Thus, the final analysis was based on 23 patients (aged 21–49 years, mean = 37.7 years; standard deviation [SD] = 9.6); 8 reported no history of CM and 15 reported a history of CM according to our criteria.

The groups did not differ with regard to age and diagnosis, and there was no significant difference in severity of depressive symptoms, although the CM group in tendency exhibited higher Beck's Depression Inventory (BDI) scores. Descriptive statistics of the groups' characteristics are reported in Table 1.

**Table 1** Description of the CM and no CM group olfactory function and OB volume

| | No CM (*N* = 8) | | CM (*N* = 15) | | |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | *P*-value |
| Age | 38.1 | 9.4 | 37.5 | 10.0 | 0.88 |
| Mean CTQ | 8 | 2.2 | 17 | 3.5 | <0.001 |
| Diagnosis | Percent | | Percent | | |
| Substance disorders (F10–F19) | 0% | | 9% | | |
| Mood (affective) disorders (F30–F39) | 100% | | 82% | | |
| Neurotic, stress-related and somatoform disorders (F40–F48) | 88% | | 100% | | |
| Behavioral syndromes associated with physiological disturbances and physical factors (F50–F59) | 25% | | 27% | | |
| Disorders of adult personality and behavior (F60–F69) | 38% | | 55% | | |
| Behavioral and emotional disorders with onset in childhood and adolescence (F90–F98) | 0% | | 18% | | |
| | Median | Range | Median | Range | |
| BDI questionnaire | 27 | 31 | 34 | 32 | 0.09 |
| Olfactory threshold | 10.1 | 6.5 | 6.8 | 6 | <0.001 |
| Olfactory discrimination | 14 | 3 | 12 | 7 | 0.1 |
| Olfactory identification | 15 | 6 | 13.5 | 5 | 0.013 |
| | No CM (*N* = 6) | | CM (*N* = *14*) | | |
| Olfactory bulb volume right | 59.3 | 19.5 | 50.6 | 46.4 | 0.18 |
| Olfactory bulb volume left | 62.8 | 21.1 | 50.6 | 46.4 | 0.03 |
| Olfactory bulb volume highest | 64.6 | 21.1 | 52.7 | 46.4 | 0.026 |
| Olfactory bulb volume averaged | 61.2 | 18.2 | 50.5 | 46.4 | 0.048 |

The grouping was carried out according to the CTQ questionnaire. Both groups did differ significantly in olfactory threshold and olfactory identification, and in the left, the averaged and in the best OB volume.

### Material

The magnetic resonance imaging measurements were performed with a 1.5-Tesla scanner (Sonata Vision; Siemens) using an 8-channel-head coil as described previously (Negoias et al. 2010). Each participant was scanned with a whole brain anatomical sequence (5-mm-thick standard T1-weighted 3-dimensional [3D] sequence) to rule out organic brain disorders. The OB sequence included acquisition of 2-mm-thick T2-weighted fast spin-echo images without interslice gap in the coronal plane covering the anterior and middle segments of the base of the skull. All these images were analyzed by the same trained observer (S.N.), who was blind to the group category or olfactory test results. The AMIRA 3D visualization and modeling system (Visage Imaging) was used to draw left and right OBs limits on each coronal slice of the T2 images. OB volumes could be identified reliably in 6 patients without CM and 14 with CM. OB volumes were calculated by planimetric manual contouring (surface in square millimeters), and all surfaces were added and multiplied by 2 (2-mm slice thickness) to obtain a volume in cubic millimeters. The change of diameter at the beginning of the olfactory tract was used as the distal demarcation of the OB. The procedure is visualized in Figure 1. The larger of the 2 OB volumes was defined as best OB volume and was used for analyses. We based this decision on a previous study demonstrating that the nostril with the largest patency demonstrates the best fit with odor detection threshold (Frasnelli et al. 2002).

Olfactory function was assessed using the validated and reliable "Sniffin' Sticks" tests resembling pen-like odor dispensers (Burghart GmbH; compare Hummel et al. 2007). Instead of liquid dye, the tampon of the pen is filled with a liquid odorant. To present the odor, the pen's cap was removed by the experimenter for approximately 3 s, and the tip of the pen was placed 1–2 cm in front of the nostrils. The interval between presentations of individual pens from a triplet was approximately 3 s. Odor thresholds were obtained for phenyl ethyl alcohol (a rose-like odor) diluted in propylene glycol. Employing a 3-alternative, forced-choice paradigm, the participants had to identify the pen that contained the rose odor, which was presented at various concentrations. Two successive correct identifications of the pen containing the odor, or 1 incorrect identification, triggered a reversal of the staircase to the next higher or the next lower dilution step, respectively. Odor thresholds were determined as the average of the final 4 of 7 staircase reversals. In order to prevent visual cues during measurements, participants were wearing an eye mask. Odor identification was assessed by means of 32 common odors, each presented in 1 pen. Using a 4-alternative, forced-choice paradigm, identification of each individual odor was performed from a written list of 4 descriptors. The test result was the sum of correctly identified odors (Haehner et al. 2009).

Depression severity was measured by the German version of BDI (Hautzinger et al. 1995; Beck et al. 1996).

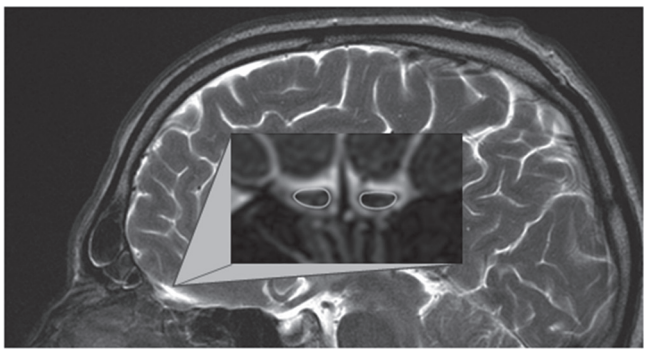

**Figure 1** Example of an OB. The OB is located bilateral at the inferior frontal part of the brain. OB limits are drawn on each coronal slice using the AMIRA 3D visualization and modeling system (Visage Imaging).

### Statistical methods

Data were analyzed using SPSS version 20 (SPSS Inc.). Due to the relatively small sample size, distribution-free statistical analysis was performed (Mann–Whitney *U* test). Alpha level was set at 0.05, 2-tailed. Because depression is known to alter OB volume (Negoias et al. 2010), BDI scores were added as covariate to an ordinal regression with best OB volume as dependent and group as independent factor.

The correlation between olfactory function and OB volume was analyzed using partial correlation with the mean CTQ score as covariate.

### Ethics statement

The study followed the Declaration of Helsinki on Biomedical Research Involving Human Subjects and was approved by the ethics committee from the Technical University of the Dresden Medical School. All participants provided written informed consent.

## Results

A significant reduced OB volume in the CM group was found for the best OB ($Z = 2.2$, $P = 0.026$, compare Figure 2) and the left OB ($Z = 2.1$, $P = 0.033$), but not for the right OB ($Z = 1.4$, $P = 0.18$). The effect remained significant for the best OB volume, after adjusting for depression (chi square = 6.24, $P = 0.044$).

A significantly reduced olfactory threshold and odor identification were found in patients with CM compared with patients without CM (threshold $Z = 3.4$, $P < 0.001$, see Figure 3; identification $Z = 2.5$, $P = 0.013$). However, there was no significant difference in odor discrimination.

A trend was found for the correlation between the olfactory threshold and the left OB volume ($r = 0.41$, $P = 0.082$), but not for the right or the best OB volume (OB volume right $r = 0.22$; OB best $r = 0.34$). There was no significant correlation between the OB volume and olfactory discrimination or identification ($r = -0.02$ – $r = 0.17$).


**Figure 2** OB volume in patients with ($N$ = 14) and without ($N$ = 6) CM. A significantly reduced OB volume was found in patients with CM.

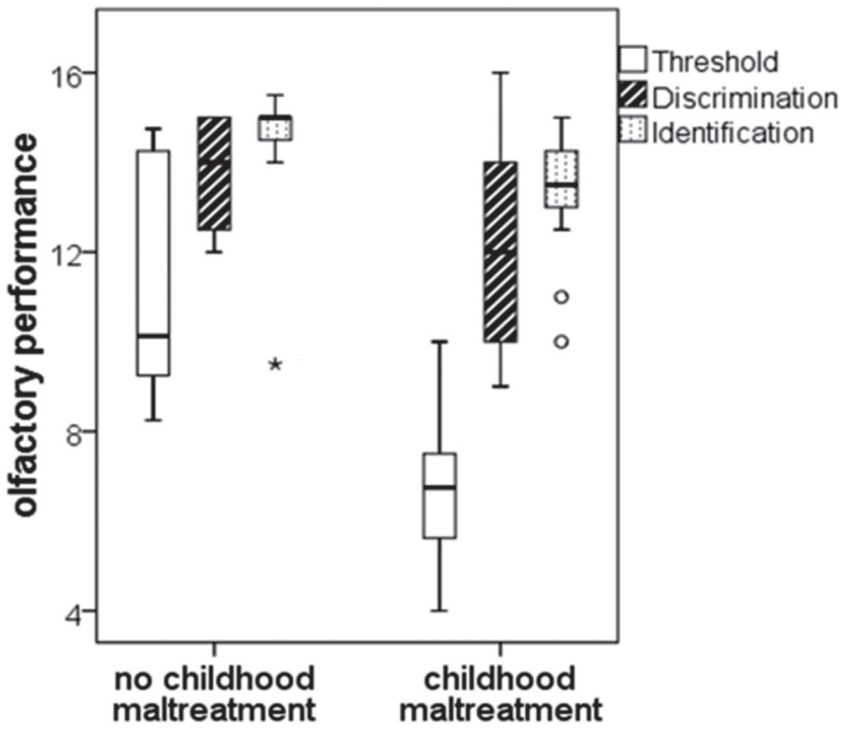


**Figure 3** Olfactory performance in patients with ($N$ = 15) and without ($N$ = 8) CM. A significantly reduced olfactory threshold and identification was found in patients with CM.

## Discussion

Our data revealed that women with a major disruption in the sensitive childhood development phase exhibit reduced OB volume. In the CM group, the best OB volume was decreased by 20% compared with the controls. The OB seems to be one of the structures, apart from the hippocampus and the medial prefrontal cortex (van Harmelen et al. 2010; Teicher et al. 2012), that is negatively affected in at least some patients with CM. In line with this, olfactory threshold and identification were reduced in women with CM. The olfactory discrimination test points in the same direction, but missed statistical significance. Olfactory function in

humans is partially dependent on OB volume (Yousem et al. 1999; Buschhuter et al. 2009); however, the aforementioned reduced hippocampus and prefrontal cortex volume might also contribute to reduced olfactory performance in women with a history of CM.

We are aware of the restrictions in our study: First, the sample size is rather small. This limits interpretation of the results, and furthermore, large effects only can be detected, whereas smaller ones are missed (Cohen 1992). Another limitation addresses the use of retrospective data. The CTQ asks about CM, but it is limited to the time, the participants can remember. The critical time of olfactory neuroplasticity might be located in early childhood (Sanai et al. 2011), a time before explicit remembrance.

Careful to these limitations, we want to provide 2 alternative explanations for the results: 1) Major stress during childhood development affects the neurogenesis at the human OB in a way as has been shown in animal studies previously (Hitoshi et al. 2007). It seems reasonable that neurogenesis is disturbed by aversive environmental conditions, but whether significant postnatal neurogenesis at the OB exists at all in humans is still under debate (Rakic 2002; Breunig et al. 2007; Curtis et al. 2007; Pignatelli and Belluzzi 2011; Sanai et al. 2011; Bergmann et al. 2012). 2) Our result may be specific to the sample of depressed patients and persons with a history of CM and smaller OB volume are over-represented such a sample. A smaller OB volume might be a factor of vulnerability for development of psychosomatic diseases in the presence of major stressors. The OB projects into the amygdala, a structure highly important for emotional processing. Reduced OB volume could cause diminished input into this structure. A volumetric study based on rodents, presumed that a complete removal of the OB induces dysfunction in the cortical-hippocampal-amygdala circuit, which has a major role in stress reaction (Song and Leonard 2005). For humans, Pause et al. (2001) argue that a dysfunctional state of the OB accounts for altered emotional processing by inhibitory projections from the human OB to the amygdala (Pause et al. 2001). However, based on our data, we cannot draw conclusions about the cortical-hippocampal-amygdala circuit, and other areas not analyzed in this study may also be involved. It has been shown previously that depressive patients exhibit smaller OB volume and lower olfactory function than healthy controls (Negoias et al. 2010). Comparing our data with this study, the OB volume of depressed patients without CM is in the range of normal controls, whereas the OB volume of depressed patients with CM is below the group of mixed-depressed patients. Our data open the gate to further research in this field: Studies performed among young children who are victim of childhood abuse, or not, can clarify if there is difference the early OB development. Further studies on adults, on the other hand, should include a group of nondepressed persons with CM.

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