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REDUCED OLFACTORY BULB VOLUME AND OLFACTORY SENSITIVITY IN PATIENTS WITH ACUTE MAJOR DEPRESSION

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Abstract—The purpose of this study was to assess olfactory function and olfactory bulb volume in patients with acute major depression in comparison to a normal population. Twenty-one patients diagnosed with acute major depressive disorder and 21 healthy controls matched by age, sex and smoking behavior participated in this study. Olfactory function was assessed in a lateralized fashion using measures of odor threshold, discrimination and identification. Olfactory bulb volumes were calculated by manual segmentation of acquired T2-weighted coronal slices according to a standardized protocol. Patients with acute major depressive disorder showed significantly lower olfactory sensitivity and smaller olfactory bulb volumes. Additionally, a significant negative correlation between olfactory bulb volume and depression scores was detected. Their results provide the first evidence, to our knowledge, of decreased olfactory bulb volume in patients with acute major depression. These results might be related to reduced neurogenesis in major depression that could be reflected also at the level of the olfactory bulb.

Key words: olfaction, smell, major depression, olfactory bulb, olfactory sensitivity.

In recent years a series of studies has investigated olfactory function in various neuropsychiatric disorders (for review see Atanasova et al., 2008). Motivating this research is the partial overlap between emotional and olfactory brain structures, especially the limbic system and prefrontal areas. Dysfunctions in emotional processing areas are consequently expected to also affect the olfactory perception. In turn, olfactory probes could provide a surrogate measure of some neuropsychiatric symptoms.

Olfactory deficiencies have been established in schizophrenia (Turetsky et al., 2009a) whereas in affective disorders a review of the literature research provides controversial results. Major depression is one such case, with results covering almost the entire spectrum of olfactory testing outcomes. Odor identification ability ranges from normal (Amsterdam et al., 1987; Warner et al., 1990; Lombion-Pouthier et al., 2006; Swiecicki et al., 2009) to decreased performance (Serby et al., 1990), compared to a normosmic control group. For threshold measurements, one study reported no difference and no correlation between olfactory sensitivity and depression quantification scales for patients with acute depression, but better sensitivity for patients after 42 days after initiation of treatment (Gross-Isseroff et al., 1994) supporting the results from an earlier study (Serby et al., 1990). In line with these results, Swiecicki et al. showed no olfactory sensitivity impairments in unipolar depression (Swiecicki et al., 2009). On the contrary, Pause and colleagues reported strongly reduced olfactory sensitivity in acute-phase major depressive disorder (MDD) that correlated negatively with depression scores. When investigating the same group of patients after successful therapy, no olfactory sensitivity difference was found compared to controls (Pause et al., 2001). The same dynamic was in cerebral processing as assessed by reduced amplitudes of olfactory event related potentials (ERPs) peaks in patients with MDD at the beginning of the therapy, without reproduction of the effect after successful treatment (Pause et al., 2003). Decreased olfactory sensitivity in MDD has been replicated in a recent study (Lombion-Pouthier et al., 2006). Seasonal affective disorder studies have also studied the relationship between olfactory function and depression, with the same contrasting results. One study reported no difference in olfactory thresholds and identification between patients and controls (Postolache et al., 1999), while another showed better thresholds for patients, regardless of season (Postolache et al., 2002).

It seems that the relationship between olfaction and depression is reciprocal. Olfactory impairment alters the quality of life (Hummel and Nordin, 2005); loss of olfactory function is typically associated with increased depressive symptoms (Deems et al., 1991; Gudziol et al., 2009a; Seo et al., 2009). A recent report showed depressive symptoms correlate negatively with olfactory sensitivity in healthy participants (Pollatos et al., 2007) analogous to the results of Pause et al. on patients with MDD (Pause et al., 2001). The question whether olfactory impairment alone could lead to or trigger a major depression episode remains to be answered. Two considerations are crucial when trying to investigate olfactory function in MDD. First, it is important to discriminate between testing patients with acute depression and patients in a remission, or between medicated and unmedicated patients. Differences in methodological approaches, number of participants and heterogeneity in

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Abbreviations: BDI, Beck's depression inventory; MDD, major depressive disorder; OB, olfactory bulb; SD, standard deviation; SVZ, subventricular zone.

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medication and moment of testing could account for the inconsistencies in results seen in previous studies.

Second, some authors divide olfactory function tests into those focusing on peripheral processing (threshold measurement) and those focusing on cognitive processing (e.g., odor discrimination or odor identification; Cain, 1979), concluding that they should be examined separately. Most of the studies investigating olfactory function in MDD used identification tests, mainly the University of Pennsylvania Smell identification Test (UPSIT). While olfactory identification scores correlate with olfactory thresholds (Doty et al., 1984; Hummel et al., 1997), independent testing of various olfactory functions could provide information on the level of the interaction between olfaction and depression. On one hand, cognitive impairment associated with major depression could interfere with odor identification or discrimination abilities (Austin et al., 2001; Marvel and Paradiso, 2004). On the other hand, it has been shown that bulbectomized rodents provide a model for depression (Song and Leonard, 2005), with correction of symptoms after chronic administration of antidepressants. The authors of this study presumed that bulbectomy induced dysfunction in the cortical-hippocampal-amygdalar circuit, responsible for modulating behavioral responses. Specifically, the olfactory bulb (OB) sends inhibitory projections to the amygdala, which is involved preferentially in the processing of fear and sadness (Costafreda et al., 2008). In light of these ideas some authors have speculated that in MDD, dysfunction at the level of the olfactory bulb could cause not only the reduced olfactory sensitivity, but also the increased sadness and fear, through disinhibition of the amygdala (Pause et al., 2001).

The human OB is a highly plastic structure whose volume reflects changes in olfactory sensitivity, as shown in patients with post-traumatic chemosensory deficits (Yousem et al., 1996a, 1999; Rombaux et al., 2006), post-infectious olfactory deficits (Mueller et al., 2005b; Rombaux et al., 2006), congenital anosmia (Yousem et al., 1996b; Abolmaali et al., 2002), neurodegenerative disorders (Mueller et al., 2005a) and in normosmic participants (Yousem et al., 1998). A recent study provided normative data in a normosmic population (Buschhuter et al., 2008). To our knowledge, no study has yet been published addressing the connection between the OB and depression in humans.

The purpose of the present study was to assess olfactory function and OB volume in patients with acute MDD compared to a normal population matched for age, sex, and smoking behavior, using a standardized test for odor threshold, discrimination and identification.

EXPERIMENTAL PROCEDURES

Participants and experimental protocol

The study was performed in accordance to the Declaration of Helsinki on Biomedical Studies Involving Human Subjects (World Medical Association, 1997) and was approved by the University of Dresden Medical Faculty Ethics Review Board. All participants provided written informed consent before inclusion in the study.

Twenty-five inpatients of the Clinic for Psychosomatic Disorders and 22 healthy controls were invited to participate in this study. All patients had been admitted to the hospital and treated because of acute MDD. They had been previously diagnosed with acute MDD by the treating physician /clinical psychologist (KP) after completing a Composite International Diagnostic Interview (CIDI, DIA-X German version; Wittchen and Pfister, 1997) according to DSM IV criteria. Healthy controls were recruited via posters set in the University Clinic area and reimbursed for their participation. Before proceeding with olfactory and volumetric measurements, the testing protocol for all participants included a detailed medical history review as well as otorhinolaryngological examination, comprising nasal endoscopy, which ensured exclusion of nasal or internal pathology potentially causing olfactory dysfunction. All participants underwent a mini mental state examination (MMSE; Folstein et al., 1975) to screen for possible cognitive impairment. Additionally, all participants were asked to complete the German version of Beck's Depression Inventory (BDI; Beck et al., 1961 German version; Hautzinger et al., 1995) and to rate their olfactory function on a 7 points scale ranging from "extremely bad" to "very good."

Four patients were excluded because of concomitant nasal pathology or existence of comorbidities known to interfere with olfactory function (severe septum deviation, sinonasal disease). The final group included four men and 17 women, aged between 21 and 55 years (mean±standard deviation (SD)=36.86±10.13 years); 14 were non-smokers, and seven smokers. Demographic and illness-related parameters are shown in Table 1. Comorbidities included: somatoform disorders (12 cases) posttraumatic stress disorder (nine cases) and anxiety disorders (17 cases). Medication of the patients included selective serotonin reuptake inhibitors (SSRI: Citalopram, Escitalopram, Paroxetine) in five cases, tricyclic antidepressants in three cases (Mirtazapin, Doxepin, Primipramin), serotonin-norepinephrine reuptake inhibitors (SNRI: Venlafaxin) in three cases, anticonvulsants in seven cases (Carbamazepin, Pregabalin, Valproat), one with zinc and one with lithium. Additionally four patients received neuroleptic drugs (Risperidon and Quetiapin), as well as analgesics (five cases) and proton pump inhibitors (three cases), while five patients were free of medication.

One subject from the control group was excluded because of presumption of incidental MRI findings and failure to complete required tests. The final control group was composed out of 6 males and 15 females, aged between 20 and 52 years (mean±SD= 39.62±11.39 years), including 19 non-smokers and two smokers. None of the controls scored higher than nine on the BDI questionnaire (mean±SD=3.12±2.91) or reported psychiatric diagnoses in their personal history. Data for part of the control group (15 participants) were randomly selected according to age groups from a database of a previous study that followed the same inclusion criteria as the present study (Buschhuter et al., 2008).

The groups did not differ in terms of age ($T_{40}=0.83$, $P=0.41$), sex distribution (Chi-square=.52, $P=0.47$) and smoking habits (Chi-square=4.30, $P=0.12$) but significantly differed regarding BDI scores ($T_{40}=-9.8$, $P<.001$).

Olfactory function was assessed using the "Sniffin' Sticks" test battery (Burghart GmbH, Wedel, Germany) following a standard-

Table 1. Demographic and illness related parameters for patients ($n=21$)

	Minimum	Maximum	Mean	SD
BDI	11	51	29.67	10.84
Age (y)	21	55	36.86	10.13
Age at debut of disease (y)	9	42	20.25	9.65
Duration of disease (y)	2	40	15.70	11.88
Duration of current episode (d)	16	75	43.55	19.95