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Research Report

Olfaction as a marker for depression in humans

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ABSTRACT

Background: Animal studies show a strong link between the loss of olfactory function and depressive behavior. We analyzed, whether olfactory function is a marker for depression in humans. If so, reduced olfactory function can be expected in depression that improves to level of normality after successful antidepressive treatment.
Methods: Twenty-seven female in-patients with depression were compared to 28 healthy age-matched women at the beginning and at the end of antidepressive therapy or at two visits, respectively. Olfactory function was assessed comprehensively including threshold, discrimination and identification testing, chemosensory event related potentials and olfactory functional magnetic resonance imaging.
Results: At the beginning of psychotherapy the patients exhibited reduced olfactory discrimination, prolonged latencies of the event-related potential and reduced activation in secondary olfactory structures (thalamus, insula, and left middle orbitofrontal). After therapy, patients improved significantly in all of the parameters and consequently the differences between control group and patients vanished.
Limitations and conclusion: We conclude that olfaction is a marker for depression. However, the results are limited to a relatively selective sample of depressed women.

1. Introduction

Depression is a common disease affecting about 8–12% of the world population at least once in their life (Andrade et al., 2003). Depression is mainly characterized by depressed mood, loss of interest and fatigue (WHO, 2010), which is accompanied by brain alterations in the prefrontal limbic network (Liu et al., 2012), involving the orbitofrontal cortex, anterior and posterior cingulate cortex, insula, amygdala, hippocampus and thalamus (Hoflich et al., 2012). Those regions overlap with regions involved in olfaction. In the last years studies accumulate showing that olfactory processing and depression are linked. Therefore it has been concluded, that reduced olfactory ability could be a marker for depression (Atanasova et al., 2008; Pause et al., 2003).

The connection between olfaction and depression was first described in the rodent model, where bilateral destruction of the olfactory bulb induces altered serotonin and dopamine concentrations (Masini et al., 2004), resulting in depression-like behavior (Kelly et al., 1997a; Leonard, 1984a; Song and Leonard, 2005). It is not clear, if the results can be transferred to humans. However, patients with olfactory loss (Deems et al., 1991; Temmel et al., 2002) or congenital anosmia (Croy et al., 2012) are more likely to exhibit signs of depression.

On the other side, depressed patients exhibit reduced olfactory threshold, identification and discrimination ability (Atanasova et al., 2010; Negoias et al., 2010, Pause et al., 2001; Lombion-Pouthier et al., 2006). Additionally, olfactory processing, as analyzed with chemosensory event-related potentials, has been found to be reduced in depression (Pause et al., 2003). After successful depression treatment olfactory threshold and chemosensory processing appears to normalize (Pause et al., 2001, Pause et al., 2003). It can therefore be assumed that depression reduces the processing and perception of the resulting olfactory information. Consequently, one would expect alterations in the activation of primary and secondary olfactory areas. However, this has – to the best of our knowledge – never been examined. Furthermore, processing of olfactory stimuli should normalize after remission of depression, if olfactory ability is a marker for depression.

We investigated olfactory activation in depressed vs. healthy people before and after anti-depressive therapy. To obtain a comprehensive view about olfactory processing and perception in depression, functional magnetic resonance imaging as well as

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psychophysical and chemosensory event related testing was performed.

2. Materials and methods

2.1. Sample

Initially, 31 women with depression or adjustment disorder were tested at the beginning and at the end of psychotherapy. Five of those were excluded from the analysis because major depression was not the leading diagnosis. Data is presented for 27 patients with major depression (aged between 22 and 59 years, mean 38.5, SD 10.6) that were tested at the beginning and at the end of psychotherapy and compared to 28 healthy women (aged between 22 and 56 years, mean 35.3, SD 10.3).

The two groups did not differ significantly in age ($t[54]=1$, $p=0.33$). Descriptive statistics of the groups' characteristics and diagnoses are reported in Table 1. None of the participants reported severe neurological disorders and acute or chronic nasal diseases in an anamnestic interview.

At first contact depressed patients were in-patients at the Clinic of Psychosomatic and Psychotherapy of the Technical University Hospital Dresden; all of them had a history of severe childhood maltreatment. The patients were preselected by detailed anamnestic interviews which were performed by trained psychotherapists in the Clinic of Psychosomatic and Psychotherapy. All of the patients were diagnosed with major depressive disorder. Inpatient treatment had a mean duration of 82 ($\pm$16) days. The mean duration between patient assessments 1 and 2 was 68.5 ($\pm$11) days.

The control group had no prior or planned inpatient or outpatient psychotherapy or other medical procedures during the investigation period. The mean duration between assessment 1 and 2 was 86.2 ($\pm$12) days, which was significantly longer than for the patients ($p<0.01$).

The patients exhibited enhanced depression in the Becks Depression Inventory (BDI (Beck and Steer, 1987; Hautzinger et al., 1995)) and Hamilton depression scale (Hamilton, 1960; CIPS, 1996), before and after therapy, compared to the controls (BDI: $t[54]=13.7$; Hamilton: $t[54]=12.0$; both: $p<0.001$, compare Table 1). However, depression severity as measured with the Hamilton Depression Scale was reduced after psychotherapy ($t[26]=2.8$, $p=0.011$).

All of the participants received psychophysical olfactory testing at both visits. Seventeen of the patients and 16 of the controls additionally underwent electrophysiological olfactory testing and 14 of the patients and 13 of the controls underwent olfactory functional magnetic imaging (fMRI) at both visits. There were no significant differences between patients who did and who did not participate in the electrophysical or fMRI testing with regard to age and depression as accessed by BDI and Hamilton depression scale. In addition, there were no significant differences in olfactory threshold, discrimination and identification ability between these two portions of the group. The same was true for control subjects.

2.1.1. Psychophysical testing

Odor thresholds, identification and discrimination ability were obtained with a validated and reliable forced-choice paradigm using the Sniffin Sticks testing kit (Burghart GmbH; compare (Bult et al., 2007)). For olfactory threshold assessment, phenyl ethyl alcohol (PEA, a rose-like odor) diluted in propylene glycol was used (Croy et al., 2009). Olfactory identification was assessed by means of 32 common odors (Haehner et al., 2009).

2.1.2. Electrophysiological olfactory testing

Chemosensory event-related potentials (CSERP) were recorded after monorhinal chemosensory nasal stimulation, performed with a specifically devised stimulator (Olfactometer OM2S, Burghart Instruments, Wedel, Germany) that allows administration of chemical stimuli without causing concomitant mechanical or thermal sensations. Chemical stimuli of 200 ms duration were embedded in a constantly flowing air stream (8 l/min) applied to the nasal cavity through a canula with an inner diameter of 4 mm inserted approximately 1 cm into the nostril beyond the nasal valve area. Temperature and humidity of the air stream was kept constant (36.5 °C, 80% relative humidity). Rise time of the stimulus concentration was less than 20 ms. PEA (40% v/v) and H_2S (4 ppm) were used for olfactory, CO_2 for trigeminal stimulation. Both odors are considered to induce little or no trigeminal by-activation and differ in pleasantness: PEA is known to be perceived as pleasant, H_2S smells like rotten eggs and is perceived unpleasant (Croy et al., 2010; Hummel et al., 2000). Importantly, at this concentration the odors differ in pleasantness, but not in intensity (Croy et al., 2013a).

Each participant received 20 stimuli of each quality in blocks of five stimuli, presented randomly across the entire recording

Table 1
Descriptive characteristics of the patients and control group.

	Time	Control group		Patients	
		Mean	SD	Mean	SD
Age		35.3	10.3	38.5	10.6
BDI Depression Questionnaire	Before	3.7	3.8	31.2	9.3
	After	3.3	4.1	27.8	11.7
Hamilton Depression Score	Before	3.4	3.7	25.4	8.7
	After	3.4	3.9	22.2	9.7
Diagnosis (before)					
				Number	Percent (%)
Major depression	Depressive episode (F32)			4	15.4
	Recurrent depressive disorder (F33)			22	84.6
Neurotic, stress- related and somatoform disorders	Phobic anxiety disorders (F40)			6	23.1
	obsessive compulsive disorder (F42)			4	15.4
	posttraumatic stress disorder (F43.1)			23	88,5
	Adjustment disorders (F43.2)			2	7.7
	somatoform disorders (F45)			9	34.6
	dissociative disorders (F44)			2	7.7
Behavioral syndromes – eating disorders (F50)				2	7.7
Disorders of adult personality and behavior (F60)				9	34.6