



Odor-related brain hyper-reactivity in euthymic bipolar disorder: An fMRI and ERP study

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ABSTRACT

Previous studies on olfactory function in patients with bipolar disorder (BD) are limited and contradictory. The current study aimed to comprehensively analyze the olfactory function of patients with euthymic BD using psychophysical, electrophysiological and neuroimaging techniques. Twenty-one patients with BD in remission and 20 healthy controls were tested with the “Sniffin’ Sticks” olfactory test. Block-design fMRI data to a pleasant and an unpleasant stimulus were acquired while recording intensity and hedonic ratings. Olfactory event-related potentials (OERP) to the same stimuli were additionally recorded. Results show no differences between patients and healthy controls in terms of self-rated olfactory function and tested olfactory domains (odor threshold, discrimination or identification) ($p > 0.05$). Compared to healthy controls, patients showed an increased fMRI activation in multiple cortical and subcortical regions as a response to olfactory stimulation, as well as larger amplitudes of OERPs regardless of the hedonic valence of the odor. All in all, patients with euthymic BD showed a stronger central responsiveness to odorous stimuli in fMRI and OERPs despite of normal psychophysical results, indicating the probable existence of an odor-related over-reactive brain network in the remission phase of BD.

1. Introduction

Social behavior and adaptation to the environment, altered to various extents in a range of affective disorders, are modulated by brain areas that receive perceptual input (Mesulam, 1998; Phillips et al., 2003a, b). Among all sensory modalities, olfaction has a unique position because of its intimate connection with emotion through overlapping processing circuits in the anterior limbic network (ALN), which includes prefrontal regions and subcortical structures such as the thalamus, striatum and amygdala (Mega et al., 1997; Ongur and Price, 2000). A reciprocal interaction between olfaction and emotion has been described: odors strongly influence mood, while emotional states have been shown to induce olfactory perceptual changes (Chen and Dalton, 2005; Pollatos et al., 2007). In fact, multiple studies concluded that olfactory deficits might be a marker of some psychiatric conditions (Atanasova et al., 2008; Croy et al., 2014; Croy and Hummel, 2016; Naudin et al., 2012). Indeed, odors might constitute a unique probe to

evaluate emotional processing circuits in patients with affective dysfunctions (Chen et al., 2018a,b; Ehrlichman, 1992; Hinton and Henley, 1993).

In bipolar disorder (BD), dysfunctions occur in the overlapping areas olfactory and emotional circuits in the ALN (Brambilla et al., 2005; Frazier et al., 2005; Strakowski et al., 2005a,b). Different stages of BD have been associated with structural abnormalities in the prefrontal cortex (PFC), striatum and amygdala, while numerous functional studies characterizing mainly the manic or depressive phases of BD have suggested reduced prefrontal modulation of subcortical and medial temporal structures within the ALN, leading to mood dysregulation. Considering the close anatomical and functional relationship between olfactory information processing and emotional regulation, studies of olfactory function seem to be of particular interest in further exploring the central abnormalities connected with BD. Nonetheless, there are few studies focussing on olfaction and BD, in contrast to major depression (Chen et al., 2018a,b; Croy et al., 2014; Negoias et al., 2016;

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Pabel et al., 2018) and schizophrenia (Gur et al., 1999; Moberg and Turetsky, 2003; Turetsky et al., 2009). Kazou et al. recently reviewed 15 studies on olfaction in BD and suggested that patients with BD suffer from significant olfactory deficits (Kazour et al., 2017), and the olfactory function of BD patients is significantly associated with psychotic symptoms (Striebel et al., 1999) and social functioning (Hardy et al., 2012; Lahera et al., 2016). Moreover, studies on nasal biopsies of patients with BD suggested significant apoptosis of olfactory neuroepithelial progenitor cells (McCurdy et al., 2006; Schroeder et al., 2016), abnormalities of the cell cycle and phosphatidylinositol signalling pathway (McCurdy et al., 2006) and underexpression of the BRAF gene and protein (Schroeder et al., 2016). In addition, the mRNA levels of the GSK3 β and CRMP1 genes in BD patients' olfactory neuroepithelium were significantly associated with BD status and with the severity of mood changes (McLean et al., 2018). However, few studies have focused on the olfactory-related central-level dysfunctions of patients with BD. Takahashi demonstrated reduced depth of the bilateral olfactory sulci in patients with BD (Takahashi et al., 2014) and Krueger observed reduced N1 peak latencies of olfactory event-related potentials (OERPs) in a subgroup of patients with event-triggered episodes (Kruger et al., 2006). Neither of these studies included electrophysiological and neuroimaging measurements simultaneously, and the neural mechanisms behind the olfactory deficit of BD patients remain unclear. In addition, whether olfactory deficits are a state or trait marker of patients with BD is still in dispute. Kazour's review summarized evidence that olfactory deficits might be a state marker of mood syndromes in BD (Kazour et al., 2017), but changes in olfactory function have also been described in the remission phase of BD (Kruger et al., 2006; Lahera et al., 2016).

In line with evidence that people rarely fully recover from BD, clinical observations suggest that many patients with BD in remission present subsyndromal symptoms that point towards increased affective reactivity and mood instability (Dargel et al., 2018; Kurtz and Gerraty, 2009; M'Bailara et al., 2009). Functional imaging studies confirm such clinical observations, revealing regional changes in the ALN that are present during otherwise non-symptomatic disease stages and might represent risk factors for developing further disease episodes (Kruger et al., 2003; Malhi et al., 2007, 2005; Strakowski et al., 2004, 2005a,b). Some studies report the existence of baseline ALN hyperactivity in not only emotion-dependent but also emotion-independent contexts during euthymia (Liu et al., 2012; Strakowski et al., 2004, 2005a,b; Townsend et al., 2010), while others describe an ongoing overall attenuation of brain activity compared to that of healthy subjects (Brady et al., 2017; Malhi et al., 2005, 2007). Many researchers in the field appear to have accepted the concept of perseverance of diminished prefrontal modulation of limbic structures resulting in dysregulation of mood, even during euthymia.

The aim of this study was to investigate olfactory function in patients with euthymic BD psychophysically and especially in terms of central processing by means of electrophysiological and neuroimaging measurements. This approach was chosen to form a comprehensive picture of olfactory processing in euthymic BD patients, including the recording of equivalents of the early and late processing of olfactory information, and the holistic perception of olfactory stimuli. In accordance with the studies suggesting persistent over-reactivity in remission, we hypothesized the presence of a more vigorous response to odors in BD patients than in healthy controls at a central level, especially in the ALN.

2. Methods

2.1. Subjects

The experiments took place at the University of Dresden Medical School. The study was performed in accordance with the requirements of the Declaration of Helsinki on Biomedical Studies in Human Subjects

and was approved by the Institutional Review Board of the Dresden Medical School (protocol number EK254102008). Written informed consent was obtained from all participants.

Twenty-seven outpatients of the Clinic of Psychiatry (16 females and 11 males), aged 22–56 years (mean age 35.6 years, standard deviation [SD] 8.2 years), were asked to participate in the study. Twenty-five patients had been diagnosed with BD type I, and 2 with BD type II. The BD diagnoses were issued by the treating psychiatrist according to the DSM-IV criteria. Remission (euthymia) was defined as an absence of symptoms of depression, hypomania/mania or mixed mania for a minimum of 6 months without recurrence. This was assessed through a review of clinical records and an interview conducted by an experienced psychiatrist. In addition, participants with BD completed the Young Mania Rating Scale and the Hamilton Depression Scale, with score criteria of ≤ 6 and ≤ 4 , respectively, for inclusion in the study. The medications being taken by the patients included atypical antipsychotics (quetiapine in 10 cases, olanzapine in 1 case, risperidone in 2 cases, ziprasidone in 1 case), serotonin-norepinephrine reuptake inhibitors (SNRIs: venlafaxine in 1 case, duloxetine in 1 case), anticonvulsants (carbamazepine in 2 cases, valproate in 2 cases), lithium in 6 cases, and dopamine agonists (aripiprazole in 1 case), while 8 patients were free of medication. Patients with other Axis I or II diagnoses or who were receiving treatment with drugs known to influence olfactory function were not included in the study. Demographic and illness-related parameters are summarized in Table 1.

Twenty-two healthy, normosmic subjects (12 females and 10 males) aged between 25 and 53 years (mean age 34.5 years, SD 8.26 years) formed the control group. The experimental and control groups did not differ in terms of age ($T_{48} = -0.44, p = 0.46$) or sex distribution (chi squared = 0.11, $p = 0.74$) but differed in terms of smoking habits (chi squared = 4.70, $p = 0.03$). Smoking was consequently included as a covariate for further analysis. Control subjects were recruited using posted announcements within the university hospital campus. Participants received moderate financial compensation for their participation. The exclusion criteria for both the patient and control groups were age under 18 years, a history of severe neurological or medical comorbidity, significant head trauma, drug abuse, history of any disease suspected to have a significant impact on olfactory function (e.g., diabetes, Parkinson's disease, renal failure), acute or severe chronic rhinitis or sinusitis, and relevant otorhinolaryngological pathology that could interact with olfactory function. Additional exclusion criteria for the control group consisted of any past or present psychiatric diagnosis (Axis I and II) and family history of psychiatric illnesses. Subjects were assessed by taking a structured medical history and conducting an otorhinolaryngology clinical examination, including nasal endoscopy.

Participants were asked to rate their olfactory sensitivity using an 8-

Table 1
Demographic and psychophysical data for patients with bipolar disorder and healthy controls. TDI is the sum of scores of olfactory threshold, discrimination and identification.

	Patients	Controls
Total no. of subjects	27	22
Sex	Male	11
	Female	10
	16	12
Mean age (years, SD)	35.63 (8.23)	34.5 (8.26)
Minimum age (years)	22	25
Maximum age (years)	56	53
Diagnosis (no. of patients)	BD I	25
	BD II	2
Age at onset (years, SD)	24.4 (4.5)	NA
Mean number of episodes	Mania or	4.8
	Hypomania	NA
No. of subjects tested	26	19
TDI score right (SD)	33.4 (3.2)	32.1 (4.9)
TDI score left (SD)	33.1 (2.9)	32.2 (3.2)

point scale ranging from “complete loss” to “excellent”. Information about smoking behavior and exposure to toxic substances was also collected. Five patients and 1 control subject were smokers. Normosmia was tested separately for each nostril using the “Sniffin’ Sticks” test battery.

Two experiments were performed in separate sessions a maximum of 3 weeks apart. Experiment 1 consisted of OERP recordings, while Experiment 2 comprised fMRI measurements. All subjects completed a handedness test (Oldfield, 1971) as well as a standard inventory of MRI exclusion criteria. Only right-handed subjects who did not fulfil any of the named fMRI exclusion criteria were enrolled. Subjects were asked not to eat or drink anything but water or to smoke for two hours prior to testing and not to wear perfume on the day of the experiments.

2.2. Olfactory assessment

Before we proceeded with Experiment 1, olfactory function was assessed during the first session using the “Sniffin’ Sticks” test battery (Hummel et al., 2007; Kobal et al., 2000). This battery includes measures of odor threshold (T), odor quality discrimination (D) and odor identification (I), using felt-tip pens filled with liquid odorants or odorants dissolved in propylene glycol. To present each odor, the experimenter removes the pen cap for approximately 3 s and places the tip of the pen approximately 2 cm in front of the subject's nostril. Testing was performed separately for the left (L) and right (R) nostrils in a sequence that was randomized across subjects (TR/TL, DR/DL, IR/IL). The untested nostril was sealed with Microfoam tape. Subjects were instructed to breathe in through the open nostril and out through the mouth. All measurements were performed in a quiet, air-conditioned room. For technical reasons, olfactory function could not be assessed in two patients.

2.3. Experiment 1—recordings of olfactory evoked potentials

To record OERPs, we performed chemosensory nasal stimulation using an OM2s olfactometer (Burghart Instruments, Wedel, Germany), which allows the application of chemical stimuli without concomitant mechanical or thermal sensation (Kobal and Hummel, 1988). This is achieved by embedding chemical stimuli of 250 ms duration in a constantly flowing air stream (7.2 l/min) applied to the nasal mucosa by means of a cannula with an inner diameter of 4 mm. The cannula is inserted approximately 1 cm into the nostril beyond the nasal valve area. The temperature and humidity of the air stream were kept constant (36.5 °C, 80% relative humidity). The rise time of the stimulus was less than 20 ms. Hydrogen sulphide (H₂S, 4 ppm, smell of rotten eggs) and phenyl ethyl alcohol (PEA, 40% v/v, smell of roses) were used for olfactory stimulation. Both odorants are known to activate the olfactory system with little or no simultaneous trigeminal activation (Doty et al., 1978). Sixteen presentations of each odorant were alternatively applied to the left or right nostril with an inter-stimulus interval of 20–30 s to avoid habituation (Hummel and Kobal, 2001). Participants were seated in an air-conditioned, darkened and acoustically shielded room to minimize additional sensory stimulation. During measurements of OERPs, patients also received white noise through headphones. Following each stimulus, subjects rated intensity and hedonic valence using visual analogue scales shown on a monitor in front of them. The patients' movements were monitored using a video camera system. EEG was recorded from 5 positions defined by the international 10/20 system: 3 central positions (Cz, Fz, Pz) and 2 lateral positions (C3 and C4), referenced to the linked earlobes (A1 + A2). Blink artefacts were monitored from an additional site (Fp2). Stimulus-linked EEG segments of 2048 ms were digitally recorded at a frequency of 250 Hz (0.2–30 Hz bandpass filter; off-line filtering with 15 Hz low-pass filter). OERPs were obtained through off-line averaging of the digitized EEG segments. Records contaminated by eye blinks (> 50 µV in the Fp2 lead) or other disturbances (e.g., high-frequency motor artefacts) were discarded

during off-line visual inspection of single trials. The peak OERP latencies (in relation to stimulus onset); the amplitudes of P1, N1 and P2; and the peak-to-peak amplitudes P1N1 and N1P2 were evaluated.

Data from 6 subjects (4 patients (1 female and 3 male) and 2 healthy male controls) were dropped after testing was aborted (2 patients) or the subjects blinked excessively (2 patients and 2 controls). The assessed groups (20 controls and 21 patients) did not differ in terms of sex (chi squared = 0.15, $p = 0.69$) or age ($t_{40} = 0.23$, $p = 0.82$) but differed in smoking habits (chi squared = 5.16, $p = 0.02$), and so smoking habits were used as a covariate in the subsequent analyses.

Data were analysed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). The results were examined using repeated-measures analysis of variance, adopting “side of stimulation” (left/right), “test” (threshold, discrimination, identification) and, in the case of OERP recordings, “recording site” (positions Fz, Cz, Pz, C3 and C4) and “odor” (H₂S, PEA) as within-subjects factors. The factor “group” (patients vs. controls) was used as a between-subjects factor. Degrees of freedom were adjusted with the Greenhouse-Geisser correction. Post hoc comparisons were performed using Bonferroni-corrected t-tests for dependent and independent variables. The level of significance was set at 0.05. Only significant main effects and two-way interactions will be reported.

2.4. Experiment 2—fMRI

The participants in Experiment 2 were a subset of those who participated in Experiment 1. The 11 patients who agreed to participate in Experiment 2 were included (7 males and 4 females, age range 26–47 years, mean age 36 years, SD = 7.39 years). The control group consisted of 11 subjects (6 males and 5 females, age range 25–53 years, mean age 35 years, SD = 9.83 years). No significant difference was found between the two groups in terms of age ($t_{21} = 0.07$, $p = 0.78$) or smoking habits (chi squared = 1.04, $p = 0.30$). To enable concomitant olfactory stimulation and MRI acquisition, we used a model involving delivery of odors via a computer-controlled OM6b air-dilution olfactometer (Burghart Instruments, Wedel, Germany). This allowed alternation between olfactory and non-olfactory stimulation conditions in a 20 s ON/20 s OFF block design. Stimuli were delivered for 1 s every 2 s during the ON period. Every ON period was followed by a matching baseline OFF period during which only pure air was delivered. Each of the two stimuli, H₂S and PEA, was presented in alternating blocks repeated 4 times, resulting in an overall 340 s scanning run. Each run was repeated 2 times, both to the left and to the right nostril alternatively. The order of odorant blocks in a run and the order in which the nostrils were tested were randomized across participants. A passive task was employed for distribution of stimuli. Subjects were instructed to concentrate on the odorants during the presentation of stimuli. At the end of the scanning session, subjects were asked to rate the intensity (“0” – nothing perceived to “10” – extremely intense) and hedonic value (“–5” – extremely unpleasant to “+5” – extremely pleasant) of each of the 4 conditions: PEA and H₂S, right and left. Anatomical scans were acquired for each participant prior to each functional run. The overall scanning time was approximately 35 min, and the whole fMRI session, including positioning of the subject in the scanner, lasted less than 1 h.

Data were acquired using a 1.5 T MR scanner (Sonata; Siemens, Erlangen, Germany). For anatomic overlays, a T1-weighted (turboFLASH sequence) axial scan with 224 slices, voxel size of 1.6 × 1.1 × 1.5 mm, a repetition time (TR) of 2500 ms, an echo time (TE) of 35 ms, and two averages (2500/3.93/2) was acquired. fMRI acquisitions were performed in the axial plane (oriented parallel to the planum sphenoidale to minimize bone artefacts) using a multi-slice spin-echo-planar imaging (SE-EPI) sequence. The scan parameters included a 64 × 64 matrix and a voxel size of 3 × 3 × 3.75 mm. A total of 120 images were acquired at each of 24 slice locations per paradigm.

Neuroimaging data were processed using SPM12 (Wellcome Department of Cognitive Neurology, London, UK, implemented in

Table 2

Brain areas with significantly varied activation patterns between BD patients and healthy subjects (3-way ANOVA, $p < 0.005$, cluster level 3, main effect of “group”). Data presented includes the number of activated voxels, the effect size (F), the statistical threshold (Z), the relative statistical significance threshold (p), the cluster mean coordinate in MNI system and the corresponding brain area.

Brain Area	Hemi-sphere	Brodmann area	Cluster size	Voxel F -Score	Voxel Z -Score	Voxel p (unc)	MNI coordinates
<i>Increased in BD patients</i>							
Middle Frontal Gyrus	R	10	23	24.69	4.48	0.000	36 42 15
Inferior Frontal Gyrus	R	10	7	14.13	3.41	0.000	51 24 15
Inferior Frontal Gyrus/OFC/Insula	R	47	10	14.06	3.40	0.000	42 18 –15
Medial Frontal Gyrus	R	10	9	12.86	3.25	0.001	9 60 6
Inferior Frontal Gyrus/OFC	L	47	5	11.50	3.07	0.001	–33 15 –21
Anterior Cingulate	L	25	18	18.32	3.88	0.000	–3 15 –3
Medial Frontal Gyrus/Anterior cingulate	L	10/32	27	16.14	3.65	0.000	–9 57 6
	R			11.05	3.00	0.001	0 51 3
	L			9.43	2.76	0.003	0 45 –3
Uncus/Amygdala	R		6	15.01	3.52	0.000	21 –6 –24
Lentiform Nucleus - Putamen	L		4	12.47	3.20	0.001	–21 6 12
Insula/Superior Temporal Gyrus	R	13/22	34	26.80	4.65	0.000	48 6 –9
	R			13.04	3.27	0.001	57 –3 –6
Insula/Superior Temporal Pole	L	13	12	11.59	3.08	0.001	–36 6 –15
	L			11.05	3.00	0.001	–42 0 –18
<i>Increased in healthy/control¹ subjects</i>							
Insula	L	13	3	10.81	2.97	0.002	–33 24 3

MATLAB 2018b; The MathWorks, Inc., Natick, MA, USA). Functional data were registered, realigned to correct for problems associated with movement and then coregistered to the corresponding structural images. Finally, the spatially normalized (stereotactically transformed into MNI ICBM152 space; MNI template supplied by SPM12) and smoothed images (by means of a $7 \times 7 \times 7$ mm³ FWHM Gaussian filter) were analysed.

First, a general linear model (GLM) modeling the on-off-stimuli period for the canonical haemodynamic function plus derivatives was performed. Hypotheses were tested using one-sample t -tests (df: 464) to explore activations following the stimuli. The analysis according to the GLM was performed on the two groups using all SPM images from each single subject analysis (random effect). A one-way three-level ANOVA was employed to check the effect of the canonical haemodynamic function and its derivative. A two-sample t -test (df: 20; $p < 0.005$, cluster level 3) was used to compare the activation differences between the two groups. Finally, a group-odor interaction analysis was performed, and the separate effects of PEA and H₂S were studied (two-sample t -test; $p = 0.005$, cluster level 3).

3. Results

3.1. Psychophysical tests

No difference was found between the two groups in terms of self-rated olfactory function (chi squared = 3.95, $p = 0.41$). None of the tested olfactory domains (thresholds, discrimination or identification) differed between patients and subjects ($p > 0.05$).

3.2. Experiment 1

3.2.1. Ratings

Due to technical issues, intensity ratings were obtained consistently throughout the OERP recordings from 18 controls and 13 patients. Hedonic ratings, however, were obtained from 20 controls and 21 patients. ANOVA of intensity and hedonic ratings, employing “odor” (PEA/H₂S) and “side” (left/right) as the within-subjects factors, “group” (patients/controls) as the between-subjects factor and “smoking habits” as a covariate, showed no significant differences between groups. However, a significant effect of the factor “odorant” in the case of hedonic ratings ($F_{(1,41)} = 208.14$, $p < 0.001$) was observed, with H₂S being rated more negatively than PEA.

3.2.2. Electrophysiological responses

Latency analyses did not provide significantly different results for within- or between-group comparisons. Generally, the amplitudes appeared to be larger in the patient group than in the control group. A significant effect of the factor “group” was found for P1N1 peak-to-peak amplitude in response to both PEA ($F_{40} = 8.12$, $p < 0.01$) and H₂S ($F_{40} = 8.77$, $p < 0.01$).

3.3. Experiment 2

3.3.1. Group differences in olfactory function

The subset of patients and healthy controls participating in Experiment 2 did not differ significantly in terms of self-rated or measured olfactory function; neither individual nostril assessment nor “best nostril” varied significantly between the two groups ($p > 0.1$).

3.3.2. Ratings

All participants rated the four conditions (rose-left, rose-right, H₂S-left and H₂S-right) as equally intense ($p > 0.1$). In both groups, a significant difference was found between the hedonic ratings of the two odors. An analysis of variance of the hedonic ratings, adopting “side of stimulation” (left/right) and “odor” (PEA/H₂S) as within-subjects factors and “group” (control/patients) as the between-subjects factor, revealed a significant main effect of “odor” (Wilks’s lambda = 0.101, $p < 0.001$) and a trend towards significance for the “group” variable ($F_{40} = 4.17$, $p = 0.055$), with patients rating PEA as less pleasant and H₂S as more unpleasant than controls.

3.3.3. fMRI results

The main effect of “group” in a 3-way ANOVA ($p < 0.005$, cluster level 3) revealed the amygdala, anterior insula, ventral anterior cingulate cortex (VACC) (BA 24/25), dorsal ACC (BA 32) and ventro-lateral PFC (middle and medium FG, BA 10 and 11), superior temporal gyrus (STG), inferior frontal gyrus (IFG) and dorsal striatum (pallidum) as regions with significantly different activation patterns between patients and healthy subjects. A relative increase in activation in controls was observed in only one cluster in the insula. The remainder showed higher activation in patients than in controls (Table 2, Fig. 1). Specifically, t -test analysis between “patients” (P) and “controls” (C), regardless of odor quality and side of stimulation, showed numerous activated voxels in the P > C contrast, much more than in the C > P contrast. The results from both contrasts are shown in Table 3. Specifically, in the P > C contrast, the amygdala showed bilateral activation,

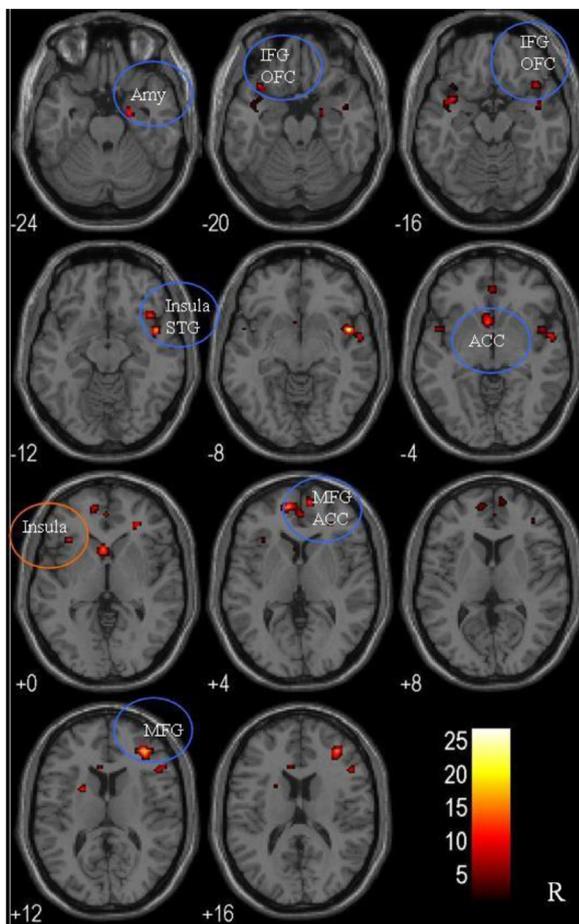


Fig. 1. Series of axial sections with clusters showing differences in activation between BD patients and healthy subjects (main effect of “group”, 3-way ANOVA, $p < 0.005$, cluster level 3, R-right). Blue and orange circles surround regions of increased activation in patients and in healthy subjects group, respectively. Labels indicate the amygdala – Amy, inferior frontal gyrus- IFG, orbitofrontal cortex – OFC, medial frontal gyrus - MFG, middle frontal gyrus - MiFG, anterior cingulate cortex – ACC, superior temporal gyrus – STG, insula, caudate. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

as did the hippocampus and parahippocampal gyrus; the ACC was activated on the left side. Furthermore, in this contrast, the PFC showed extensive activation in BA 47 and BA 10 bilaterally. The region showing the largest signal variation between patients and healthy subjects was the left PFC. A PFC volume of approximately 729 mm^3 , with its center of mass at $(-12, 54, 3)$ in the MNI coordinate space, corresponds to the MFG (BA 10). For the reverse contrast, $C > P$, activated areas included clusters in the insula, left fusiform gyrus and right amygdala.

The next step of the analysis was to investigate group-odor interactions. The results of 2-sample t -test analyses for PEA and H_2S are shown in Tables 4 and 5, respectively. For the pleasant odorant PEA (Fig. 2, Table 5), the control group showed preferential activation of the right OFC (BA 47) as well as the pars triangularis of the left inferior frontal gyrus (BA 10). Patients showed more extensive activation than healthy subjects; the activated regions included the PFC (BA 10), left insula, caudate body, and STG; strengthened activation was also observed in limbic structures such as the bilateral amygdala and right hippocampus. Overall, data acquired during presentation of the usually unpleasant odorant H_2S (Fig. 3, Table 4) showed the same predominant activation in the patient group as in the control group. In the $C > P$ contrast, only a cluster in the right amygdala emerged at the threshold level employed. This was not found in the equivalent contrast using data acquired during PEA presentation. In contrast, when compared to

healthy subjects, patients showed extensive activation in the PFC (BA 10, 11 and 47); in limbic structures (bilateral ACC (BA 24/32) and bilateral amygdala); and in the bilateral insula, caudate head, and STG.

4. Discussion

This is the first study comprehensively analysing the olfactory function of patients with euthymic BD in the aspects of psychophysics, electrophysiology and functional neuroimaging. The main findings of this study were as follows:

- Patients with euthymic BD neither showed significant differences compared to healthy controls in olfactory thresholds, discrimination or identification, and they were not significantly different in terms of the intensity and hedonic ratings of odors;
- Patients with euthymic BD responded more vigorously to odors than controls did, as demonstrated by a higher P1N1 amplitude of OERPs, regardless of the hedonic valence of the odor;
- Patients with euthymic BD exhibited increased fMRI activation as a response to both pleasant and unpleasant olfactory stimuli and regardless of the side of stimulation in multiple cortical and sub-cortical brain regions that are part of olfactory or emotion processing circuits.

The most remarkable observation is the discrepancy between the increased central response to odors reflected in both fMRI and OERP and the otherwise normal performance in olfactory function tests and normal ratings of odor intensity and hedonic value. These results are in line with the previous literature on BD in remission, reporting persistent central abnormalities accompanied by subclinical signs of affective lability – seen in both emotional and non-emotional contexts, despite clinical remission (Kurtz and Gerraty, 2009).

Olfaction is, in this context, a unique probe of particular interest: of all senses, olfaction, through its hedonic dimension (Yeshurun and Sobel, 2010) and through its extensive anatomical and functional connections to the limbic system, can induce strong emotional reactions (Larsson et al., 2014; Schiffman, 1974) and seems to be an excellent trigger for the exploration of the functionally overlapping emotional processing circuits. Evidence points towards affective values dominating olfactory perception, with affective valence being the main perceptual correlate of odorous molecules (Khan et al., 2007; Yeshurun and Sobel, 2010). Consequently, hedonic value is the main dimension of olfaction and the determinant of its affective charge (Yeshurun and Sobel, 2010). The discrepancy between central processing and normal psychophysical olfactory measurements in our study may result from an over-responsive emotional processing circuit in the remission phase of BD, entering action when confronted with a potential emotional situation, eventually leading to controlled affective responses and behaviors. Specifically, this would imply an increase in the effort necessary to identify the emotional meaning of stimuli and thus to differentiate between relevant and irrelevant emotional stimuli, then produce adequate responses, enabling patients to cognitively regulate and maintain their behavioral responses to the stimuli (Phillips et al., 2003b). This concurs with findings that euthymic patients with BD have higher affective lability and experience everyday emotions with a higher intensity than controls, as assessed with self-rating scales (Henry et al., 2008). A previous study demonstrated that patients with euthymic BD and a history of event-triggered episodes exhibited shorter OERP N1 peak latencies than euthymic BD patients without such a history, suggesting a disinhibition of orbitofrontal areas involved in the processing of emotional events in patients with BD (Kruger et al., 2006).

In line with earlier results from smaller sample sizes, the current study indicated that euthymic patients with BD had more-vigorous OERP responses than normal controls did, suggesting there may be odor-related brain hyper-reactivity in patients with BD. Regarding the fMRI results, when we investigated the main effect of “population”,

Table 3

Contrast: Patients vs Healthy subjects” and “Healthy subjects vs. Patients” over all conditions (2-sample *t*-test, $p < 0.005$, cluster level 3). Data presented includes the number of activated voxels, the statistical threshold (*T*), the relative statistical significance threshold (*p*), the cluster mean coordinate in MNI system and the corresponding brain area.

Brain area	Hemi-sphere	Brodmann area	Cluster size	Voxel Tscore	Voxel p(unc)	MNI coordinates
Patients vs. Healthy subjects						
<i>Frontal lobe</i>						
Orbitofrontal	R	47	6	4.47	0.000	30 30 –18
Medial Frontal Gyrus	R	10	6	3.59	0.001	9 60 6
Medial Frontal Gyrus	R	10	5	3.36	0.002	36 42 15
Medial Frontal Gyrus	R	10	6	3.61	0.001	33 39 15
Medial Frontal Gyrus	L	10	27	4.27	0.000	–12 54 3
Inferior Frontal Gyrus/Insula	L	47	10	3.69	0.001	–51 21 –3
<i>Sub-lobar</i>						
Caudate Head						
Anterior Cingulate	R		19	4.62	0.000	9 24 12
Caudate Head (Olfactory)	R		16	3.73	0.001	0 6 0
	L			3.3	0.002	–6 15 –3
<i>Limbic lobe</i>						
Uncus/Amygdala Parahippocampal Gyrus	L		14	4.52	0.000	–18 –9 –24
Uncus/Amygdala	L			3.57	0.001	–24 0 –27
Anterior Cingulate						
Caudate Head	L	24	11	4.31	0.000	–9 24 12
	L			3.5	0.001	–15 24 6
Anterior Cingulate	L	32	8	4.02	0.000	–3 39 9
Parahippocampal Gyrus						
Hippocampus	R		10	4.04	0.000	27 –12 –18
Parahippocampal Gyrus						
Amygdala	R		9	3.61	0.001	21 –9 –24
Parahippocampal Gyrus	R	28		3.18	0.002	27 –9 –30
<i>Temporal lobe</i>						
Superior Temporal Gyrus/Insula	R	38 /13	77	5.2	0.000	45 18 –30
Superior Temporal Gyrus	R			4.55	0.000	30 9 –24
Fusiform Gyrus	R	20		4.19	0.000	39 –3 –30
Superior Temporal Gyrus	R	38	13	4.54	0.000	54 0 –9
Fusiform Gyrus	R	20	6	3.77	0.001	51 –15 –24
Middle Temporal Gyrus	R	21	6	3.39	0.001	51 6 –36
Middle Temporal Gyrus	L	21	12	4.64	0.000	–51 3 –39
Healthy subjects vs. Patients						
<i>Sub-lobar</i>						
Insula						
Insula	L	13	9	5.71	0.000	–33 24 3
Amygdala	R		4	3.15	0.003	27 –6 –12
<i>Temporal lobe</i>						
Fusiform Gyrus						
Fusiform Gyrus	L	20	7	3.87	0.000	–39 –15 –30

clusters in the amygdala, anterior insula, VACC (BA 24/25) and VLPFC (middle and medium FG, BA 10 and 11) but also DACC (BA 32), STG, IFG and dorsal striatum (pallidum) showed significantly stronger activation in the patient group than in the control group. All these structures are central parts of the emotional circuits. Specifically, the amygdala, insula, ventral striatum, VACC and ventral PFC are often highlighted in tasks involving appraisal of the emotional significance of a stimulus and the production of affective states, while more dorsal structures (the VLPFC, DLPFC, DMPFC, and DACC) and the hippocampus are primarily implicated in emotional regulation (Phillips et al., 2003). Such increased activation in emotional processing structures (the VLPFC, amygdala, and parahippocampus) has been previously described for euthymic BD in response to a non-emotional task (Strakowski et al., 2005a,b).

Further support for this hypothesis comes from the separate analysis of responses to pleasant and unpleasant stimuli. Again, compared to controls, patients exhibited increased activation in the bilateral OFC and VLPFC (BA 10, 11 and 47). This activation was even stronger for the unpleasant than for the pleasant odor. The control group showed significantly greater activation for the pleasant odorant PEA in a region of BA 10 corresponding to the pars triangularis of the left inferior frontal gyrus. In addition, following exposure to the unpleasant odorant H₂S, increased activation for the healthy group compared to the BD group was found in a cluster in the insula and one in the amygdala as well as in the hippocampus. This pattern seems to fit the previous literature (Urry et al., 2006, 2009). Studies of cognitive reappraisal and

suppression have revealed the existence of a network comprising regulatory cortical regions, mainly the PFC, and apparently downregulated limbic areas, including the amygdala and insula, thought to govern emotional regulation (Goldin et al., 2008; Ochsner et al., 2002; Quirk and Beer, 2006). These authors propose that failure of emotion regulation is the mechanism underlying mood disorders, especially BD, through disinhibition of limbic areas following malfunction of the inhibitory PFC (Campbell-Sills and Barlow, 2007). Using PET, OFC hypoactivity has been described in euthymic BD patients at rest and after induction of a sad mood (Kruger et al., 2003, 2006). Decreased activity in the VLPFC (BA 11/47) has been shown in all phases of BD (Blumberg et al., 2003) and reconfirmed in euthymic BD (Strakowski et al., 2005a,b) during a Stroop task after induction of a sad mood (Kruger et al., 2006) or after viewing positive and negative words (Malhi et al., 2007). VLPFC (BA 10/47) activity increases together with a decrease in MFC (BA 11) activity after performance of a non-emotional attentional task and has also been described in euthymic BD patients (Strakowski et al., 2004).

We found extensive activation in the BD patient group after exposure to an unpleasant odor, while, following a pleasant odor experience, OFC and IFG activation was found to be decreased in patients. On the other hand, there were clusters of increased activity in other regions of the VLPFC (BA 10) for the same group. The tasks administered to the subjects in the scanner might have been a confounding factor. Some authors describe a series of regions, including the ventral PFC, IFG, temporal pole, retrosplenial cortex, ACC, PCC, and angular

Table 4

Contrast „Patients vs Healthy subjects” and “Healthy subjects vs. Patients” for H2S (2-sample *t*-test, $p < 0.005$, cluster level 3). The tables show the number of activated voxels, the statistical threshold (*T*), the relative statistical significance threshold (*p*), the cluster mean coordinate in MNI system and the corresponding brain area.

Brain area	Hemi-sphere	Brodman area	Cluster size	Voxel T-score	Voxel p(unc)	MNI coordinates
Patients vs. Healthy subjects						
<i>Frontal lobe</i>						
Inferior frontal gyrus	R	47	11	4.52	0.000	42 18 –15
Inferior Operculum	R	44	7	3.93	0.000	45 12 12
Middle Frontal Gyrus/Orbitofrontal	R	10	8	3.89	0.000	27 48 0
Middle Frontal Gyrus	R	10	5	3.25	0.002	33 39 15
Medial Frontal Gyrus	L	10	5	3.89	0.000	–12 54 3
Medial Frontal Gyrus/Orbitofrontal	L	10/11	9	3.43	0.001	–3 54 –15
	L			3.14	0.003	–3 45 –9
<i>Limbic lobe</i>						
Anterior Cingulate	R	24/32	46	4.79	0.000	3 30 12
	R	32		4.09	0.000	6 33 3
	L	24		3.51	0.001	–9 29 15
Uncus/Amygdala	L	28	7	3.25	0.002	–30 6 –24
Amygdala/Uncus	R		5	3.15	0.003	24 0 –24
<i>Sub-lobar</i>						
Insula	L	13	7	4.44	0.000	–27 18 15
Insula	R	13	17	3.61	0.001	42 9 –9
Caudate head	L		28	3.9	0.000	–6 6 –3
Caudate head	R			3.34	0.002	3 9 –3
<i>Temporal lobe</i>						
Superior Temporal Gyrus	L	38	7	5.07	0.000	–48 12 –18
Superior Temporal Gyrus/Middle Temporal Gyrus	R	21/22	8	4.56	0.000	57 –3 –9
Healthy subjects vs. Patients Sub-lobar						
Amygdala/Hippocampus	R		5	3.4	0.001	21 –3 –12

gyri, with increased default activity in the resting state and during passive perception as well as decreased activity during attention-demanding cognitive tasks (Gusnard et al., 2001; Mckiernan et al., 2006; Raichle et al., 2001). Moreover, a correlation between resting-state activity in some of the mentioned regions and subjects' emotional state has been shown (Zald et al., 2002). The idea that cognitive activity can attenuate appraisal or expression of emotions has been suggested in a range of studies (Derryberry, 1988; Posner and Rothbart, 1998).

A passive task was chosen in the present study for the delivery of stimuli in the scanner: subjects were instructed to let themselves be influenced by the odorants in an attempt to avoid effortful generation of affect and the inconveniences associated with a parallel cognitive task. That the subjects spontaneously categorized and evaluated the odorants is to be presumed, especially since subjects had previously participated in the electrophysiological part of the experiments, where they were asked to judge olfactory intensity and hedonic value. Furthermore, even for passive perception, there is evidence for the engagement of semantic

circuits (Savic and Berglund, 2010). Nevertheless, as Ehrlichman and Bastone stated, olfaction is a particular case, as stimuli are first processed in limbic structures and therefore short-circuit the neocortical level of cognitive analysis to a greater extent than the other sensory modalities (Ehrlichman, 1992). This could imply that less cognitive input is needed for evaluating the emotional meaning of olfactory stimuli than stimuli of other modalities. Consequently, this observation needs to be taken into consideration when interpreting imaging results based on tasks involving cognitive demands, and it could partially explain the increased extent of activation in the PFC, temporal pole, and ACC found within the patient group in the present study.

A series of limitations must be considered when interpreting the results of this study. Chronic medication use may influence cerebral blood flows and thus account for some of the differences observed. The low number of subjects did not allow us to analyse the effects of medication. Future studies with larger sample sizes should be conducted. Only patients who were able to cooperate with our tests were

Table 5

Contrast „Patients vs. Healthy subjects” and “Healthy subjects vs. Patients” for PEA (2-sample *t*-test, $p < 0.005$, cluster level 3). The tables show the number of activated voxels, the statistical threshold (*T*), the relative statistical significance threshold (*p*), the cluster mean coordinate in MNI system and the corresponding brain area.

Brain area	Hemi-sphere	Brodman area	Cluster size	Voxel TScore	Voxel p(unc)	MNI coordinates
Patients vs. Healthy subjects						
<i>Frontal lobe</i>						
Middle Frontal Girus	R	10	21	5.35	0.000	36 39 15
Medial Frontal Girus	L	10	6	3.98	0.000	–12 57 9
<i>Limbic lobe</i>						
Hippocampus	R		15	4.11	0.000	30 –12 –18
Amygdala	R			4.09	0.000	21 –6 –21
ParaHippocampal Amygdala	L	28	4	3.34	0.002	–21 –12 –27
<i>Sub-lobar</i>						
Caudate Body	L		10	3.83	0.001	–3 12 12
Insula	L	13	5	3.26	0.002	–45 6 –3
<i>Temporal lobe</i>						
Superior Temporal Girus/Insula	R	38	8	3.87	0.000	48 3 –9
Healthy subjects vs. Patients						
<i>Frontal Lobe</i>						
Inferior Frontal Triangle	L	10	4	3.79	0.001	–39 39 0

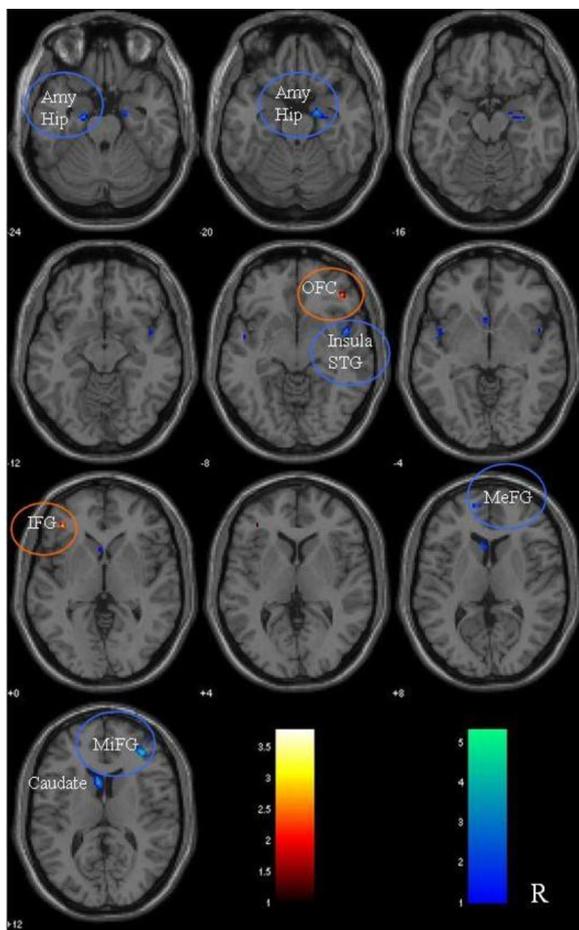


Fig. 2. Series of axial sections showing activation clusters for P vs. C (blue) and C vs. P (orange) contrasts during exposure to PEA (2 sample *t*-test, $p < 0.005$, cluster level 3, R-right). Labels indicate the amygdala – Amy, inferior frontal gyrus- IFG, orbitofrontal cortex – OFC, medial frontal gyrus - MeFG, middle frontal gyrus - MiFG, anterior cingulate cortex – ACC, superior temporal gyrus – STG, insula, caudate. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

included, and there were 8 medication-free patients in the current study, which may not completely represent the true proportion of BD patients in the clinic, as many patients with BD are on medication for life. Another confounds might result from the passive presentation of odorants inside the scanner. As discussed previously, a baseline of increased brain activity during resting and passive perception states has been described in most of the regions discussed above, while a cognitive task requiring the subjects' attention leads to decreases in activity. It can be speculated that patients could have attended the passive perception task with less interest than healthy subjects. Furthermore, information on participants' menstrual cycles was not included in the current study, which prevented us from excluding the influence of menstrual phases. Finally, it must be mentioned that no standardized interviews were used to exclude psychiatric disorders for the control group. Nevertheless, detailed subjective histories were collected, and subjects with past or present Axis I or II diagnoses were excluded.

In summary, this study highlights several regions with extended activation after exposure to a passive olfactory paradigm in patients with remitted BD, and this work also discusses the most important regions involved in emotional and olfactory processing, aiming to offer an integrative view in the context of previously published data. Nevertheless, the lack of data on central olfactory processing in the episodic stages of the disease and the scarcity of literature on further perceptual changes make it impossible to tie the changes to the stage of

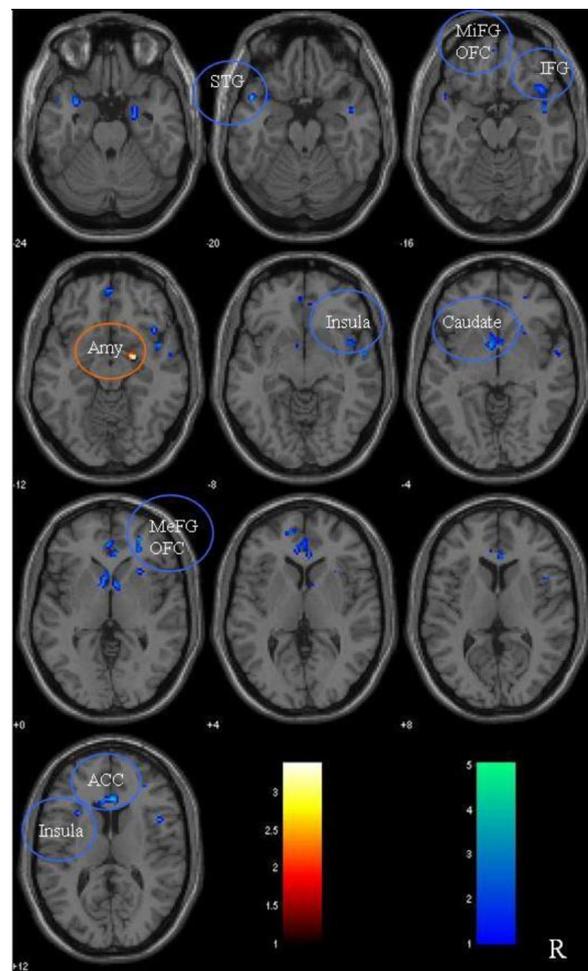


Fig. 3. Series of axial sections showing activation clusters for P vs. C (blue) and C vs. P (orange) contrasts during exposure to H2S (2 sample *t*-test, $p < 0.005$, cluster level 3, R-right). Labels indicate the amygdala – Amy, inferior frontal gyrus- IFG, orbitofrontal cortex – OFC, medial frontal gyrus - MeFG, middle frontal gyrus - MiFG, anterior cingulate cortex – ACC, superior temporal gyrus – STG, insula, caudate. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the disease or the sensory modality. Future studies should address these points, especially the particular regional differences in olfactory and emotional sub-circuits.

Furthermore, the current study investigated olfactory processing in patients with euthymic BD compared to healthy controls. No significant differences in terms of overall olfactory function or ratings of odorous stimuli were found. Nevertheless, patients reacted to olfactory stimulation more vigorously than controls did, as reflected by increased amplitudes P1N1 of the OERP and a pattern of odor-stimulated activation on fMRI in regions involved at all levels of emotion processing. The findings suggested over-reactivity in cortical and subcortical structures following passive odor exposure in euthymic BD patients, in line with other clinical and neuropsychological studies describing over-reactivity patterns during this period of disease.

5. Conclusion

Patients with euthymic BD showed increased central responsiveness to odorous stimuli despite normal psychophysical results, indicating the probable existence of a brain network that is over-reactive to odor in the remission phase of BD.

Authors disclosures

None of the authors have anything to disclose.

Ethics

The study was performed in accordance with requirements of the Helsinki Declaration on Biomedical Studies in Human Subjects and was approved by the Institutional Review Board of the Dresden Medical School (protocol number EK254102008). Written informed consent was obtained from all participants.

Role of funding source

We were free to design the study, collect the data, direct its analysis and interpretation of data, writing of report and decision to submit the article for publication without any influence from sponsors. There was no editorial direction or censorship from any sponsors.

CRedit authorship contribution statement

Simona Negoias: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **Ben Chen:** Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Emilia Iannilli:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing. **Yuping Ning:** Writing - review & editing. **Hagen H. Kitzler:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing - review & editing. **Thomas Hummel:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - review & editing. **Stephanie Krüger:** Conceptualization, Writing - review & editing.

Declaration of Competing Interest

The authors declare no conflicts of interest associated with this research study.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.06.016.

References

Atanasova, B., 2008. Olfaction: a potential cognitive marker of psychiatric disorders. *Neurosci. Biobehav. Rev.* 32 (7), 1315–1325.

Blumberg, H.P., 2003. A functional magnetic resonance imaging study of bipolar disorder: state- and trait-related dysfunction in ventral prefrontal cortices. *Arch. Gen. Psychiatry* 60 (6), 601–609.

Brady, R.J., 2017. Differential brain network activity across mood states in bipolar disorder. *J. Affect. Disord.* 207, 367–376.

Brambilla, P., 2005. Magnetic resonance findings in bipolar disorder. *Psychiatr. Clin. North Am.* 28 (2), 443–467.

Campbell-Sills, L., Barlow, D.H., 2007. Incorporating Emotion Regulation into Conceptualizations and Treatments of Anxiety and Mood Disorders. Sills, pp. 542–559.

Chen, B., 2018a. Cognitive impairment and structural abnormalities in late life depression with olfactory identification impairment: an Alzheimer's disease-like pattern. *Int. J. Neuropsychopharmacol.* 21 (7), 640–648.

Chen, B., 2018b. Interactive effect of depression and cognitive impairment on olfactory identification in elderly people. *J. Alzheimers Dis.* 66 (4), 1645–1655.

Chen, D., Dalton, P., 2005. The effect of emotion and personality on olfactory perception. *Chem. Sens.* 30 (4), 345–351.

Croy, I., 2014. Olfaction as a marker for depression in humans. *J. Affect. Disord.* 160, 80–86.

Croy, I., Hummel, T., 2016. Olfaction as a marker for depression. *J. Neurosci.* 160 (4), 1–8.

Dargel, A.A., 2018. Emotional hyper-reactivity and cardiometabolic risk in remitted bipolar patients: a machine learning approach. *Acta Psychiatr. Scand.* 138, 348–359.

Derryberry, D.R.M.K., 1988. Arousal, affect, and attention as components of temperament. *J. Pers. Soc. Psychol.* 55 (6), 958–966.

Doty, R.L., Brugger, W.P.E., Jurs, P.C., Orndorff, M.A., Snyder, P.J., Lowry, L.D., 1978. Intranasal trigeminal stimulation from odorless volatiles: psychometric responses from anosmic and normal humans. *Physiol. Behav.* 20, 175–185.

Ehrlichman, H.B.L., 1992. The use of odour in the study of emotions. In: Dodd, S.V.T.a.G. (Ed.), *The Psychology and Biology of Perfume*. Elsevier, Amsterdam, pp. 143–160.

Frazier, J.A., 2005. Magnetic resonance imaging studies in early-onset bipolar disorder: a critical review. *Harv. Rev. Psychiatry* 13 (3), 125–140.

Goldin, P.R., 2008. The neural bases of emotion regulation: reappraisal and suppression of negative emotion. *Biol. Psychiatry* 63 (6), 577–586.

Gur, R.E., 1999. Reduced gray matter volume in schizophrenia. *Arch. Gen. Psychiatry* 56 (10), 905.

Gusnard, D.A., 2001. Medial prefrontal cortex and self-referential mental activity: relation to a default mode of brain function. *Proc. Natl. Acad. Sci. USA* 98 (7), 4259–4264.

Hardy, C., 2012. Olfactory acuity is associated with mood and function in a pilot study of stable bipolar disorder patients. *Bipolar Disord.* 14 (1), 109–117.

Henry, C., 2008. Affective lability and affect intensity as core dimensions of bipolar disorders during euthymic period. *Psychiatry Res.* 159 (1–2), 1–6.

Hinton, P.B., Henley, T.B., 1993. Cognitive and affective components of stimuli presented in three modes. *Bull. Psychon. Soc.* 31 (6), 595–598.

Hummel, T., Kobal, G., 2001. Olfactory event-related potentials. *Methods and frontiers in chemosensory research*. In: S.A., Simon, M.A.L., Nicolelis (Eds.), CRC press, Boca Raton, Florida, USA, pp. 429–464.

Hummel, T., 2007. Normative data for the "Sniffin' Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. *Eur. Arch. Otorhinolaryngol.* 264 (3), 237–243.

Kazour, F., 2017. Olfactory and gustatory functions in bipolar disorders: a systematic review. *Neurosci. Biobehav. Rev.* 80, 69–79.

Khan, R.M., 2007. Predicting odor pleasantness from odorant structure: pleasantness as a reflection of the physical world. *J. Neurosci.* 27, 10015–10023.

Kobal, G., 2000. Multicenter investigation of 1,036 subjects using a standardized method for the assessment of olfactory function combining tests of odor identification, odor discrimination, and olfactory thresholds. *Eur. Arch. Otorhinolaryngol.* 257 (4), 205–211.

Kobal, G., Hummel, C., 1988. Cerebral chemosensory evoked potentials elicited by chemical stimulation of the human olfactory and respiratory nasal mucosa. *Electroencephalogr. Clin. Neurophysiol.* 71 (4), 241–250.

Kruger, S., 2003. State and trait influences on mood regulation in bipolar disorder: blood flow differences with an acute mood challenge. *Biol. Psychiatry* 54, 1274–1283.

Kruger, S., 2006. Increased olfactory sensitivity in euthymic patients with bipolar disorder with event-related episodes compared with patients with bipolar disorder without such episodes. *J. Psychiatry Neurosci.* 31, 263–270.

Kurtz, M.M., Gerraty, R.T., 2009. A meta-analytic investigation of neurocognitive deficits in bipolar illness: profile and effects of clinical state. *Neuropsychology* 23 (5), 551–562.

Lahera, G., 2016. Relationship between olfactory function and social cognition in euthymic bipolar patients. *CNS Spectr.* 21, 53–59.

Larsson, M., 2014. Olfactory LOVER: behavioral and neural correlates of autobiographical odor memory. *Front. Psychol.* 5, 312.

Liu, C.H., 2012. Abnormal baseline brain activity in bipolar depression: a resting state functional magnetic resonance imaging study. *Psychiatry Res.* 203 (2–3), 175–179.

Malhi, G.S., 2005. An emotional Stroop functional MRI study of euthymic bipolar disorder. *Bipolar Disord.* 7 (Suppl 5), 58–69.

Malhi, G.S., 2007. Reduced activation to implicit affect induction in euthymic bipolar patients: an fMRI study. *J. Affect. Disord.* 97 (1–3), 109–122.

M'Bailara, K., 2009. Emotional hyper-reactivity in normothymic bipolar patients. *Bipolar Disord.* 11, 63–69.

McCurdy, R.D., 2006. Cell cycle alterations in biopsied olfactory neuroepithelium in schizophrenia and bipolar I disorder using cell culture and gene expression analyses. *Schizophr. Res.* 82 (2–3), 163–173.

Mckiernan, K.A., 2006. Interrupting the "stream of consciousness": an fMRI investigation. *Neuroimage* 29 (4), 1185–1191.

McLean, C.K., 2018. Lithium-associated transcriptional regulation of CRMP1 in patient-derived olfactory neurons and symptom changes in bipolar disorder. *Transl. Psychiatry* 8 (1), 81.

Mega, M.S., 1997. The limbic system: an anatomic, phylogenetic, and clinical perspective. *J. Neuropsychiatry Clin. Neurosci.* 9, 315–330.

Mesulam, M.M., 1998. From sensation to cognition. *Brain* 6 (6), 1013–1052 pt.

Moberg, P.J., Turetsky, B.I., 2003. Scent of a disorder: olfactory functioning in schizophrenia. *Curr. Psychiatry Rep.* 5 (4), 311–319.

Naudin, M., 2012. State and trait olfactory markers of major depression. *PLoS ONE* 7 (10), e46938.

Negoias, S., 2016. Olfactory bulb volume predicts therapeutic outcome in major depression disorder. *Brain Imaging Behav.* 10 (2), 367–372.

Ochsner, K.N., 2002. Rethinking feelings: an FMRI study of the cognitive regulation of

- emotion. *J. Cognit. Neurosci.* 14 (8), 1215–1229.
- Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9 (1), 97–113.
- Ongur, D., Price, J.L., 2000. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cereb. Cortex* 10 (3), 206–219.
- Pabel, L.D., 2018. The impact of severity, course and duration of depression on olfactory function. *J. Affect. Disord.* 238, 194–203.
- Phillips, M.L., 2003. Neurobiology of emotion perception I: the neural basis of normal emotion perception. *Biol. Psychiatry* 54 (5), 504–514.
- Phillips, M.L., 2003a. Neurobiology of emotion perception I: the neural basis of normal emotion perception. *Biol. Psychiatry* 54 (5), 504–514.
- Phillips, M.L., 2003b. Neurobiology of emotion perception II: implications for major psychiatric disorders. *Biol. Psychiatry* 54 (5), 515–528.
- Pollatos, O., 2007. Emotional stimulation alters olfactory sensitivity and odor judgment. *Chem. Senses* 32 (6), 583–589.
- Posner, M.I., Rothbart, M.K., 1998. Attention, self-regulation and consciousness. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 353 (1377), 1915–1927.
- Quirk, G.J., Beer, J.S., 2006. Prefrontal involvement in the regulation of emotion: convergence of rat and human studies. *Curr. Opin. Neurobiol.* 16 (6), 723–727.
- Raichle, M.E., 2001. A default mode of brain function. *Proc. Natl. Acad. Sci. USA* 98 (2), 676–682.
- Savic, I., Berglund, H., 2010. Passive perception of odors and semantic circuits. *Hum. Brain Mapp.* 21 (4), 271–278.
- Schiffman, S.S., 1974. Physicochemical correlates of olfactory quality. *Science* 185 (4146), 112–117.
- Schroeder, E., 2016. The gene BRAF is underexpressed in bipolar subject olfactory neuroepithelial progenitor cells undergoing apoptosis. *Psychiatry Res.* 236, 130–135.
- Strakowski, S.M., 2004. A preliminary FMRI study of sustained attention in euthymic, unmedicated bipolar disorder. *Neuropsychopharmacology* 29 (9), 1734–1740.
- Strakowski, S.M., 2005a. Abnormal FMRI brain activation in euthymic bipolar disorder patients during a counting Stroop interference task. *Am. J. Psychiatry* 162 (9), 1697–1705.
- Strakowski, S.M., 2005b. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Mol. Psychiatry* 10 (4), 105–116.
- Striebel, K.M., 1999. Olfactory identification and psychosis. *Biol. Psychiatry* 45 (11), 1419–1425.
- Takahashi, T., 2014. Olfactory sulcus morphology in established bipolar affective disorder. *Psychiatry Res. Neuroimaging* 222 (1–2), 114–117.
- Townsend, J., 2010. fMRI abnormalities in dorsolateral prefrontal cortex during a working memory task in manic, euthymic and depressed bipolar subjects. *Psychiatry Res.* 182 (1), 22–29.
- Turetsky, B.I., 2009. Scents and nonsense: olfactory dysfunction in schizophrenia. *Schizophr. Bull.* 35 (6), 1117–1131.
- Urry, H.L., 2006. Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. *J. Neurosci.* 26 (16), 4415–4425.
- Urry, H.L., 2009. Individual differences in some (but not all) medial prefrontal regions reflect cognitive demand while regulating unpleasant emotion. *Neuroimage* 47 (3), 852–863.
- Yeshurun, Y., Sobel, N., 2010. An odor is not worth a thousand words: from multidimensional odors to unidimensional odor objects. *Annu. Rev. Psychol.* 61 (1), 219–241.
- Zald, D.H., 2002. Brain activity in ventromedial prefrontal cortex correlates with individual differences in negative affect. *Proc. Natl. Acad. Sci. USA* 99 (4), 2450–2454.