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Olfactory loss is associated with reduced hippocampal activation in response to emotional pictures

Pengfei Han [a,*], Thomas Hummel [a], Claudia Raue [b], Ilona Croy [c]

[a] Department of Otorhinolaryngology, TU Dresden, Dresden, Germany
[b] Department of Neuroradiology, TU Dresden, Dresden, Germany
[c] Department of Psychotherapy and Psychosomatik Medicine, TU Dresden, Dresden, Germany

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ABSTRACT

Emotional processing evolved within brain structures that were originally dedicated to olfactory function. Reduced olfactory function, absence of the olfactory bulb and the experimental removal of the olfactory bulb are associated with depressive behavior. Against this background, we hypothesized that olfactory dysfunction modifies the neural processing of non-olfactory emotion information. Using a functional magnetic resonance imaging design, we therefore tested whether people with and without impaired olfactory function differ in emotional perception and processing. Neural activity of 17 patients with acquired olfactory loss and 23 age- and sex-matched control participants were monitored in the MRI scanner, while they were presented with emotional and neutral pictures. Participants rated the valence and arousal for each picture after scanning. Patients showed reduced right hippocampal brain responses to emotional but not neutral pictures independent of their depressive symptoms. In addition, emotion-dependent activation in the hippocampus and insula was positively associated with the olfactory bulb (OB) volumes in healthy participants. Taken together, these findings suggest a disrupted neural processing of emotional pictures among patients with olfactory loss. This indicates a significant role of the neural olfactory trajectories for general emotion processing. Central emotion processing is reduced in olfactory disorders and relates to the OB volume in normosmic individuals.

1. Introduction

The sense of olfaction is intimately linked to emotion and olfactory perceptions are often, if not always accompanied by affective experiences (Yeshurun and Sobel, 2010; Kadohisa, 2013). The odors of flowers make people happy, "industrial" odors are typically disgusting (Croy et al., 2011), the odor of beloved ones evoke comfort (McBurney et al., 2006) and food-related odors are cross-culturally a pleasant sensation (Seo et al., 2011). Odors seem to provide an emotional background against which other stimuli are perceived. This is not surprising as olfactory processing is one of the evolutionary first ways of inter-individual communication and emotion processing evolved within brain structures that were originally dedicated to olfactory function (Northcutt, 2002). In line, the now-famous "limbic system" was not originally conceptualized as a network of emotion eloquent areas, but as a network for olfaction structures (Mac, 1950). More than 60 years later, a variety of studies shows that emotion perception is coded in a widespread network. The amygdala, right inferior orbitofrontal cortex (OFC) and the peri-aqueductal grey are involved in high-arousal emotion coding (Lindquist et al., 2012) and the anterior insula and the anterior cingulate cortex (ACC) in salience detection (Menon and Uddin, 2010). Those areas are densely interconnected and especially the hippocampus has high connectivity to the amygdala during the processing of salient stimuli (Kensinger and Corkin, 2004). Those emotional eloquent areas share function with olfactory processing, especially in the evolutionary older limbic structures (hippocampus, amygdala), the insula, OFC and ACC (Gottfried, 2010; Seubert et al., 2013; Fjaeldstad et al., 2017).

The shared function between olfactory and emotion eloquent areas were also suggested by studies in depressed individuals. In rats, the experimental removal of the first central olfactory relay, the olfactory bulb (OB) causes depression-like behavior (Redmond et al., 1997; Xu et al., 2005) and a decreased structural connectivity to subsequent structures, such as the hippocampus and amygdala (Carlsen et al., 1982). In humans, an aplastic or hypoplastic OB is not only related to anosmia,

Abbreviations: BOLD, blood oxygen level dependent.

* Corresponding author.
E-mail address: pengfeihan88@gmail.com (P. Han).

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but also to enhanced vulnerability to depression (Negoias et al., 2010) and even in non-anosmic individuals, the volume of the OB is related to depression (Negoias et al., 2010; Rottstädt et al., 2018). Consequently, olfaction is discussed as a biomarker for depression (Atanasova et al., 2008; Croy and Hummel, 2017) and we hypothesized that the constant stream of olfactory based activation, provided with every breath we take, balances neural activation of limbic structures (Croy and Hummel, 2017). In line with this assumption, central emotion processing should be altered in people with olfactory loss.

Olfactory loss, a disorder characterized by increased odor threshold and decreased accuracy for odor discrimination and identification, is accompanied by structural and functional alterations of the central olfactory system. Olfactory disorders, such as sinunasal or post-infectious diseases, are related to a reduced volume of the OB (Rombaux et al., 2006) and a decreased grey matter density in the amygdala, piriform cortex, hippocampus and insula (Bitter et al., 2010; Yao et al., 2014; Gellrich et al., 2018; Han et al., 2017). In response to olfactory stimulation, patients with such disorders have a reduced BOLD signal increase in the very same areas (Levy et al., 1999; Hummel et al., 2010; Pellegrino et al., 2016).

Combining these previous findings and the idea of an olfactory balanced emotional system, this study aimed to test whether patients with olfactory loss express a diminished neural processing of emotional stimuli. Importantly, we did not use olfactory stimuli to evoke emotions, but pictures. Central regions involved in emotional processing of pictures are identical with those involved in general emotion processing and include the amygdala (Liberzon et al., 2003; Aldhafeeri et al., 2012), hippocampus (Lane et al., 1997; Aldhafeeri et al., 2012; Schlochtermeier et al., 2013), insula (Wright et al., 2004), ACC (Kensinger and Schacter, 2006; Aldhafeeri et al., 2012), OFC (Wright et al., 2004), and - due to the mode of emotion presentation - the visual cortex (Liberzon et al., 2003). Recent research even reported the involvement of the primary olfactory cortex, the piriform cortex, in the processing of emotional pictures (Schulze et al., 2017). As previous studies demonstrated that both, negative and positive events evoke emotional brain activation in areas such as the amygdala and the hippocampus (Kensinger and Corkin, 2004; Kensinger and Schacter, 2006; Lewis et al., 2007), we decided to present a variety of pictures which carry positive and negative emotional information.

We hypothesized that patients with olfactory loss as compared to age and sex-matched controls, have a) a reduced reaction to emotional pictures and b) reduced BOLD signal increase in brain regions which are dedicated to both, olfaction and emotion: the amygdala, hippocampus, insula, ACC, OFC and piriform cortex. We furthermore hypothesized that c) the quantity of olfactory function and the OB volume directly and positively relate to the BOLD signal increase evoked by the emotional pictures.

2. Materials and methods

2.1. Participants

A total of 40 normal sighted subjects participated in the study. Of those, seventeen (10 female) were patients with diagnosed olfactory dysfunction. Diagnosis of olfactory dysfunction was confirmed via a standardized procedure (Hummel et al., 2013) involving a detailed otorhinolaryngological examination including nasal endoscopy and a standardized psychophysical testing of olfactory threshold, identification, and discrimination with the “Sniffin’ Sticks” test battery (Hummel et al., 1997). Eight of the patients were classified as functionally anosmia (TDI score < 16) and 9 were hyposmic (TDI score between 17 and 28), according to the ‘Sniffin’ Sticks' normative data (Hummel et al., 2007). The causes of olfactory loss were infection of the upper respiratory tract ($n = 9$), idiopathic ($n = 5$), traumatic injuries ($n = 2$) and chronic rhinosinusitis ($n = 2$). The duration of olfactory loss varied between 0.5 and 96 months and was 21.6 months on average (please compare Supplementary Table 1 for full details). Information about medication in patients was not protocolled. Apart from the olfactory loss in the group of patients all participants were in good health. The control group consisted of 23 age- and sex-matched normosmic subjects (11 female), all of whom also underwent the same detailed medical history and psychophysical tests for olfactory function as described for the group of patients (Supplementary Table 1). This was done to ascertain normosmic function in all controls and to exclude potential nasal pathologies.

The patient and control group did hence not differ regarding age ($t_{38} = -0.89$, $p = 0.38$) and gender distribution ($\chi^2 = 0.09$, $p = 0.53$), but in terms of olfactory function ($t_{38} = 6.90$–11.84, $p < 0.001$; Table 1). This was reflected in a significantly decreased OB volume ($t_{38} = 2.34$; $p = 0.02$). Furthermore, the patients reported slightly enhanced depression scores as compared to the controls (BDI (Beck et al., 1961), German version (Hautzinger et al., 1995); $t_{34=}-2.14$, $p = 0.04$). The mean value of both groups was within the range of minimal depression. All subjects were informed about the testing procedures and provided written informed consent prior to participation. The study design was in accordance to the Declaration of Helsinki and had been approved by the Ethics Committee of the Medical Faculty Carl Gustav Carus at the Technical University of Dresden (EK363082016).

2.2. Choice of affective pictures

Ten affectively positive, ten negative, and twenty neutral pictures were chosen from the International Affective Picture System (IAPS) (Lang et al., 1997). Picture choice was guided by the normative data of the IAPS (Lang et al., 1997), positive pictures with a valence of >7 were selected; neutral with a valence of 3–7 and negative with a valence < 3. The images were selected to target the emotions of happiness (e.g. babies, wedding events), sadness (e.g. wounded bodies, famine), anger (e.g. human violence), disgust (e.g. dirty toilet) and fear (e.g. snake). A list of selected images with the identifiable code is shown in the Supplementary Table 3.

2.3. fMRI study design

Images were presented during one functional run (10min and 53sec) using E-Prime Professional (Version 2.0, Psychology Software Tools, Inc., Pittsburgh, USA; www.pstnet.com/eprime). Each picture was displayed on a black background for 3 s. To minimize expectation effects, the interstimulus interval was varied between 12000 ms and 15000 ms with a fixation cross displayed (Fig. 1A). Each of the 40 pictures was presented once; the order of pictures was randomized within the run and between participants. After the end of the MRI session, participants reported for each image the valence from 1 (very negative) to 9 (very positive) and arousal from 1 (not arousing) to 9 (very arousing) on a paper-and-pencil rating task, based on the Self-Assessment Manikin rating system (Bradley and Lang, 1994). Rating data were available for 22 healthy controls and 16 patients (compare Supplementary Table 1). Participants were asked not to eat or drink (water excepted) 2 h before the test.

2.4. MRI data acquisition

A 3 T MRI scanner (Siemens Sonata, Erlangen, Germany) with an 8-channel head coil was used for image acquisition. A total of 217 functional images were collected per individual using a T2 single-shot echo-planar imaging (EPI) sequence: TR = 3000 ms, TE = 40 ms, 90° flip angle, voxel size 3*3*3.75 mm, no interstice gap, 192 × 192 mm Field of view. For precise normalization of the data, a high-resolution structural T1 image was acquired using a 3D magnetization prepared gradient rapid acquisition gradient echo (MPRAGE) sequence (TR = 2530 ms, TE = 2.34 ms, 256 × 256 mm Field of view, voxel size 1*1*1 mm). The

Table 1
Characteristics of healthy controls and olfactory loss patients.

	Whole sample			fMRI sample		
	Control (n = 23)	Patient (n = 17)	Comparisons	Control (n = 18)	Patient (n = 16)	Comparisons
Age (years)	53.2 ± 1.8	56.0 ± 2.7	$t_{38} = -0.89$, $p = 0.38$	54.2 ± 1.9	55.9 ± 2.8	$t_{32} = -0.52$, $p = 0.61$
Female/Male	12/11	10/7	$\chi^2 = 0.09$, $p = 0.53$	10/8	9/7	$\chi^2 = 0.002$, $p = 0.97$
Depression score (BDI II)	2.4 ± 0.6	7.4 ± 2.1	$t_{38=} -2.57$, $p = 0.01$	2.7 ± 0.7	7.8 ± 2.2	$t_{32=} -2.32$, $p = 0.03$
Odor threshold (in dilution steps)	8.7 ± 0.6	3.1 ± 0.7	$t_{38} = 6.90$, $p < 0.001$	8.9 ± 0.6	2.9 ± 0.7	$t_{32} = 6.71$, $p < 0.001$
Odor discrimination (number correctly identified out of 16)	12.6 ± 0.3	7.2 ± 0.7	$t_{38} = 8.47$, $p < 0.001$	12.8 ± 0.4	6.9 ± 0.7	$t_{32} = 8.07$, $p < 0.001$
Odor identification (number correctly identified out of 16)	13.9 ± 0.3	6.4 ± 0.8	$t_{38} = 11.84$, $p < 0.001$	13.9 ± 0.3	5.7 ± 0.7	$t_{32} = 11.36$, $p < 0.001$
Combined tests score ("TDI score*"; in units)	35.2 ± 0.7	16.7 ± 1.8	$t_{38} = 12.45$; $p < 0.001$	35.6 ± 0.7	15.5 ± 1.6	$t_{32} = 11.66$; $p < 0.001$
Olfactory bulb volume (mm^3)	98.5 ± 3.7	76.7 ± 9.6	$t_{38} = 2.34$; $p = 0.02$	97.7 ± 4.0	77.3 ± 10.2	$t_{32} = 1.93$; $p = 0.06$

Data are means ± SEM; Olfactory performance test using Sniffin' Sticks battery; n.s. not significant; * Results of the three subsets are presented as a composite score for odor threshold, discrimination and identification (TDI score).

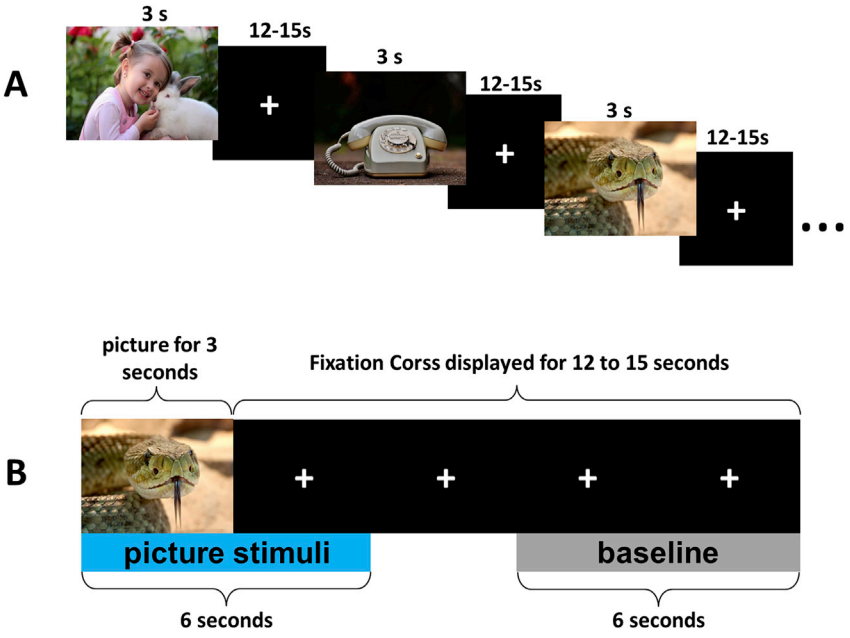

Fig. 1. The fMRI experimental design. (A) 40 pictures that differed in valence (positive, neutral, negative) were randomly presented for 3 s with an inter-stimulus interval of 12–15s. Emotional pictures from the international affective picture system were used (Lang et al., 1997). As those shall not be reprinted, similar pictures are displayed here for visualization purpose (https://www.pexels.com); (B) For each picture event, the first 6 s (including 3 s for picture display and the following 3 s fixation cross) was used as the picture stimuli, and the last 6 s period with fixation cross prior to the next picture display was taken as the baseline.

olfactory bulb (OB) imaging was performed with a fast spin-echo T2-weighted sequence covering the anterior and middle segments of the skull base (TR 58,090 ms; TE 597 ms; voxel size 2 × 2 × 2 mm^3; flip angle 1238, in total 36 contiguous slices of 2 mm thickness with no interslice gap).

2.5. Calculation of OB volumes

OB volumes were calculated based on manual segmentation of the acquired T2-weighted fast spin-echo imaging coronal data. Segmentation of the OB was performed offline using the AMIRA 3D visualization and analysis software (Visage Imaging, Carlsbad, CA, USA). The abrupt change in diameter at transition to the olfactory tract was used as the proximal differentiation of the OB (Yousem et al., 1998). Volumes were obtained by a) manual delineation slice to slice, b) addition of all slices and c) multiplying the result by the slice thickness (2 mm) to yield the overall volume in cubic-millimeters. This method had been shown to have a high reliability and accuracy (Yousem et al., 1997). OB measurements of all participants were performed by the experimenter (PH), blinded to the group category. A second rater measured OB volumes of 10 control participants and 10 patients, blinded to group category. The inter-rater correlation for control and patient groups were calculated (Pearson correlation r = 0.80, p = 0.006 for control group; r = 0.98, p < 0.001 for patient group).

2.6. Behavioral data and other statistical analyses

Statistical analyses were performed using SPSS (Version 24.0, SPSS Inc, Chicago, IL, USA), and GraphPad Prism (Version 6, GraphPad Software, Inc. La Jolla, CA). Variables were tested for normal distribution using the Shapiro-Wilk test and then compared between the two groups using independent sample *t*-test. For comparison between groups regarding valence and arousal ratings for emotional pictures first the individual ratings of the 10 positive emotional pictures, 10 negative emotional pictures and the 20 neutral pictures were averaged separately per participant. We then subtracted the ratings of the neutral from the emotional pictures to include the baseline rating. For the arousal ratings this was done by subtraction $arousal_{emo>neutral} = \left(\frac{arousal_{pos} + arousal_{neg}}{2} - arousal_{neutral}\right)$. For the valence ratings, we additionally reversely coded the negative emotional pictures $\left(valence_{emo>neutral} = \left(\frac{valence_{pos} + (10 - valence_{neg})}{2} - valence_{neutral}\right)\right.$ to avoid that positive and negative valences average themselves out. The emotional arousal and valence ratings ($arousal_{emo>neutral}$; $valence_{emo>neutral}$) were compared between groups using independent sample *t*-test (two-tailed). As both groups differed significantly in depression, the group comparison was repeated

as ANOVA under inclusion of BDI scores as a covariate. The significance level was set at $p < 0.05$.

2.7. Functional MRI data analysis

MRI data were preprocessed and analyzed using SPM12 (Statistical Parametric Mapping; Welcome Department of Cognitive Neurology, London, UK) implemented in MATLAB 2013a (Math Works, MA, USA) as follows, with the default settings unless reported otherwise: first, the functional images from each run were realigned to the first image of the first functional run and unwrapped; second, the T1-weighted anatomical image was coregistered to the averaged mean image from the realignment procedure; third, the coregistered anatomical images were segmented and the functional images were spatially normalized to the MNI space with a voxel size of 2*2*2 mm^3 using the deformation field estimated during the segmentation process; fourth, the spatially normalized EPI images were smoothed using a Gaussian kernel of 8 mm full-width at half maximum (FWHM). Finally, removal of head motion artifacts using ArtRepair (version 4, Stanford University) was applied to the preprocessed images based on the following rules: image to image motion less than 0.5 mm/TR and total images repaired less than 20%. From the original 23 controls and 17 patients who completed the fMRI scan, 6 participants were excluded due to excessive head movements ($n = 4$, including 3 controls and 1 patient) or technical problems (2 controls); thus, imaging data from 18 controls and 16 patients were included for analysis (compare Table 1 for descriptive statistics and Supplementary Table 1 for individual data).

In order to minimize sustained affective processes, the first 6 s (including 3 s for picture display and the following 3 s fixation cross) were used as picture stimuli, and the last 6 s period with fixation cross prior to the next picture display were taken as the baseline (Fig. 1B). Analyses of fMRI data were performed on two levels. On the single subject level, the following three contrasts were modeled for each participant: *Emontional*$_{\text{pos and neg pictures}}$ > *baseline*; *Neutral* > *baseline*; and *Emontional* > *Neutral* = *(Emontional*$_{\text{pos and neg pictures}}$ > baseline*)* > *(neutral* > *baseline)*. On the group level, the first-level contrasts were used to address the following statistical model: (1) one sample *t*-test for brain processing of emotional > neutral pictures in controls and in patients, separately; For those clusters which were significantly activated in response to emotional vs neutral pictures in the control group (left anterior cingulate: MNI -4 42–6, $k = 86$; right amygdala: MNI 18–2 -14, $k = 11$; left amygdala: MNI -26 -8 -12, $k = 13$), the beta values were extracted per individual using MarsBaR (http://marsbar.sourceforge.net/) and compared between control and patient groups in SPSS, controlling the BDI, age and sex; (2) two sample *t*-test to compare brain activation to emotional > neutral images between controls and patients, controlled for age, sex, and BDI scores; (3) two by two full factorial design including study group (control, patient) and condition (emotional pictures, neutral images) controlled for age, sex and BDI score in order to clarify whether there was a significant group by condition interaction. The identified cluster in this step was further explored. Therefore, we extracted the beta values within this cluster (MNI xyz = 32, −30, −6; $k = 9$) per individual and condition using MarsBaR (http://marsbar.sourceforge.net/). We continued processing this data in SPSS with a repeated measure ANOVA design with the between subject factor group (control and patients) and the within subject factor condition (emotional pictures and neutral pictures). Both main effects and the interaction effect were modeled. We did not control for depression in this analysis as the extracted values were obtained from the already BDI-corrected fMRI analysis. Post hoc tests were performed as two-tailed t-tests. In the next step (4), linear regression models were set in SPM to explore the association between brain response to emotional > neutral pictures and other measurements (OB volumes, TDI score and the duration of olfactory loss), this were performed for patients, controls and the whole participants separately. The BDI score was included as a regressor of no interest when both groups were analyzed in one model. For visualization purpose, the beta values within the identified clusters (left insula, MNI xyz = -32 -4 -14, $k = 18$; and the right hippocampus, MNI xyz = 20–28 -8, $k = 25$) showing significant correlation between the OB volume and brain response to emotional > neutral pictures in healthy participants were extracted per individual using MarsBaR (http://marsbar.sourceforge.net/).

For all aforementioned analysis steps, a region of interest (ROI) analyses approach was performed focusing on activation of brain regions involved in olfaction and emotional processing, including the piriform cortex, amygdala, hippocampus, ACC, insula, and the medial and lateral OFC. ROIs were anatomically defined with masks from the WFUPickAtlas software (ANSIR, Wake Forest University, Winston-Salem, NC, USA) (Maldjian et al., 2003) based on the "automated anatomical labeling (aal)" atlas (Tzourio-Mazoyer et al., 2002). The piriform cortex mask was derived from the AAL atlas using the "olfactory area", and all ROIs were tested simultaneously for the left and right hemispheres. Predicted responses within the ROI analyses were considered significant at peakwise FWE corrected (p_{FWE}) $p \leq 0.05$. The brain activation results from whole brain analyses are additionally reported in supplementary Tables.

2.8. Voxel-based morphometry analyses

As previous studies show positive associations between the grey matter density (GMD) and task-induced functional responses in specific regions (Takeuchi et al., 2014), the GMD was analyzed for control and patient groups using voxel-based morphometry (Ashburner and Friston, 2000). This was performed by the Cat12 toolbox (http://dbm.neuro.uni-jena.de/vbm/). Voxel-wise GMD differences between groups were examined using one-way ANOVA, controlled for age, sex and BDI score. In addition, a whole-brain correlation analysis was also performed between the GM density and BDI scores or OB volumes. For an exploratory purpose, a liberal peak level threshold of $p \leq 0.001$, uncorrected and a cluster threshold of $k \geq 10$ voxels was applied.

3. Results

3.1. Valence and arousal rating for affective pictures

Patients with olfactory loss rated the emotional images significantly less arousing than controls (arousal $_{\text{emotional>neutral}}$: $t_{36} = 2.05$, $p = 0.048$, Cohens' $d = 0.66$; Fig. 2). However, the difference turned insignificant after controlled for BDI score ($F = 1.29$, $p = 0.265$, $\eta^2 = 0.038$). There was no difference observed for the valence ratings between groups

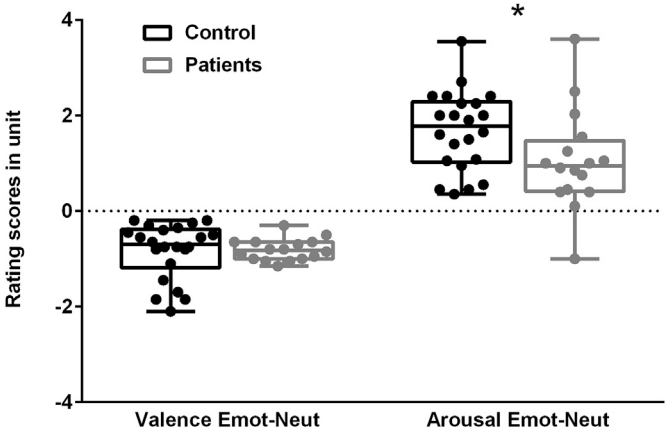

Fig. 2. Valence and arousal ratings for emotional vs. neutral pictures in patients with olfactory loss (n = 16) and controls (n = 22). Box and whiskers show the value for individual participants. Patients had a lower arousal difference between emotional vs neutral pictures compared to the controls: *Significant difference ($p < 0.05$). The difference turned insignificant ($F = 1.29$, $p = 0.265$, $\eta^2 = 0.038$) after inclusion the depression [BDI score] as covariate.

(valence $_{emotional>neutral}$: $t_{36} = -0.13$, $p = 0.90$, Cohens' $d = 0.04$; after correction for BDI scores: $F = 0.001$, $p = 0.978$, $\eta^2 < 0.001$).

3.2. Brain responses to emotional vs neutral pictures

In controls, emotional pictures as compared to neutral ones led to a significantly enhanced activation in the right hippocampus (MNI 18–4 -14, $k = 21$, $T = 6.59$, $p_{FWE} = 0.003$), left ACC (MNI -4 42–6, $k = 86$, $T = 5.53$, $p_{FWE} = 0.02$), left medial OFC (MNI -4 42–10, $k = 143$, $T = 6.67$, $p_{FWE} = 0.002$), right amygdala (MNI 18–2 -14, $k = 11$, $T = 5.32$, $p_{FWE} = 0.006$), and in tendency - in the left amygdala (MNI -26 -8 -12, $k = 13$, $T = 3.95$, $p_{FWE} = 0.056$; Table 2). In contrast, patients with olfactory loss did not show any significant activation differences between emotional and neutral pictures in the ROI analyses.

The direct comparison between study groups revealed an inferior activation of the right hippocampus in patients with olfactory loss, as compared to the controls (MNI 32–30 -4, $p_{FWE} = 0.061$, $k = 9$, Table 2) and there was no significant superior activation in patients. The whole brain analyses confirmed these results (compare Supplementary Table 4.) In line with those t-tests, the group by condition interaction effect resulted in a significant cluster in the right hippocampus (MNI 32–30 -6, $k = 9$, $T = 3.82$, $p_{FWE} = 0.040$).

The individual mean signal change in comparison to baseline was extracted from this cluster for each participant and condition and further analyzed in SPSS. The significant group by emotion interaction effect was confirmed ($F = 18.02$, $p < 0.001$, $\eta^2 = 0.22$) and explained 22% of the total task dependent BOLD signal variation within this cluster. Post-hoc comparisons showed that the hippocampal activation in response to emotional pictures was significantly smaller in the patient group as compared to controls ($t_{32} = 4.29$, $p < 0.001$, Cohens' $d = 1.46$). For neutral pictures however, the hippocampal activation did not differ between the two groups ($t_{32} = -1.08$, $p = 0.287$, Cohens' $d = 0.37$) (see Fig. 4).

For the clusters which showed significant responses to emotional vs neutral pictures in the controls group, the same tendency was observed. Patients had reduced activation to emotional pictures (individual mean signal change of emotional > baseline) than controls in the right hippocampus extending to amygdala ($F = 6.27$, $p = 0.018$, $\eta^2 = 0.18$), and in tendency in the left amygdala ($F = 3.57$, $p = 0.069$, $\eta^2 = 0.11$). The patient's activation was also slightly reduced in the left ACC extending to the mOFC, but the difference was not significant ($F = 0.944$, $p = 0.339$, $\eta^2 = 0.032$, compare Fig. 3).

Impact of the OB volume, olfactory function and duration of disease on emotional picture processing.

Over the whole group of participants, no significant association was observed between the OB volume and brain activation in the predicted ROIs. For controls however, a positive correlation was found between the OB volumes and brain responses to emotional vs neutral pictures in the left insula (MNI -32 -4 -14, $k = 18$, $T = 5.53$, $p_{FWE} = 0.035$) and the right hippocampus (MNI 20–28 -8, $k = 25$, $k = 25$, $T = 5.01$, $p_{FWE} = 0.042$) (Fig. 5). For patients, no association was found (for whole brain analyses compare Supplementary Table 5).

For the whole group of participants, the TDI score was positively associated to the BOLD signal increase in response to emotional > neutral pictures in the right ACC (MNI 12 32 14, $k = 5$, $T = 4.18$, $p_{FWE} = 0.051$). For controls, a positive correlation was found between the TDI score and brain response to emotional > neutral pictures in the ACC (MNI 8 44 18, $k = 141$, $T = 6.29$, $p_{FWE} = 0.008$). For patients, no association was found (for whole brain analyses compare Supplementary Table 6). The duration of olfactory loss within the group of patients was not significantly related to the BOLD signal increase in response to emotional vs neutral pictures in any of the ROIs (for whole brain results please compare Supplementary Table 7).

3.3. Voxel-based morphometry analyses

No significant difference for GMD between the two groups was observed. The GMD within the ROIs did not correlate to the depression scores.

4. Discussion

In controls, the processing of emotional pictures - as compared to neutral pictures - went along with an activation of the hippocampus, amygdala, and ACC. This was not observed in patients with olfactory loss. In line with the neural findings, patients reported lower arousal for emotional pictures than control participants. No such behavioral difference was observed for the valence ratings. This could be explained by ceiling effects, as the emotional pictures were selected to score high on positive or negative valence, respectively. Controlling for depression altered the behavioral results-group differences for arousal were less pronounced and missed the statistical threshold. Depression was hence included for the comparison between groups in the analysis of neural data and a significant group by condition interaction was observed in the right hippocampus.

The hippocampus is not only important for cross-modal emotional processing of chemosensory stimuli (Bensafi et al., 2013) but also involved in emotional memories (Richardson et al., 2004), such as the episodic representations of the emotional significance and interpretation of events (Phelps, 2004; Fastenrath et al., 2014) and emotional arousal information (Kensinger and Corkin, 2004; Fastenrath et al., 2014). The observed lateralization with emphasis on the right side is in line with a meta-analysis showing that the right hippocampus is more closely associated with emotional processing (Robinson et al., 2015). Our results hence suggest that olfactory disorders are functionally related to reduced emotion processing.

Moreover, even in healthy controls, olfactory projections appear to impact emotion processing, as implicated by the positive association between the OB volumes of healthy controls and hippocampal and insular activity in response to emotional vs neutral pictures. As the first central-nervous structure for olfactory processing, the OB serves as a bottleneck of central olfactory processing and its volume is related to the

Table 2
Brain activation to emotional vs. neutral pictures in control and patients: ROI analyses.

	k	T	pFWE-corrected	MNI			ROIs
				x	y	z	
Control	11	5.32	0.006	18	−2	−14	Amygdala R
	13	3.95	0.056*	−26	−8	−12	Amygdala L
	21	6.59	0.003	18	−4	−14	Hippocampus R
	86	5.53	0.020	−4	42	−6	Anterior cingulate cortex L
	143	6.67	0.002	−4	42	−10	Medial orbitofrontal cortex L
Patient	–	–	–	–	–	–	–
Control > Patient	9	4.07	0.061*	32	−30	−4	Hippocampus R
Patient > Control	–	–	–	–	–	–	–

R, right; L, left; k, cluster size in voxels; * trend significance.
For clusters with more than one peak, only the peak with the highest T value was shown.

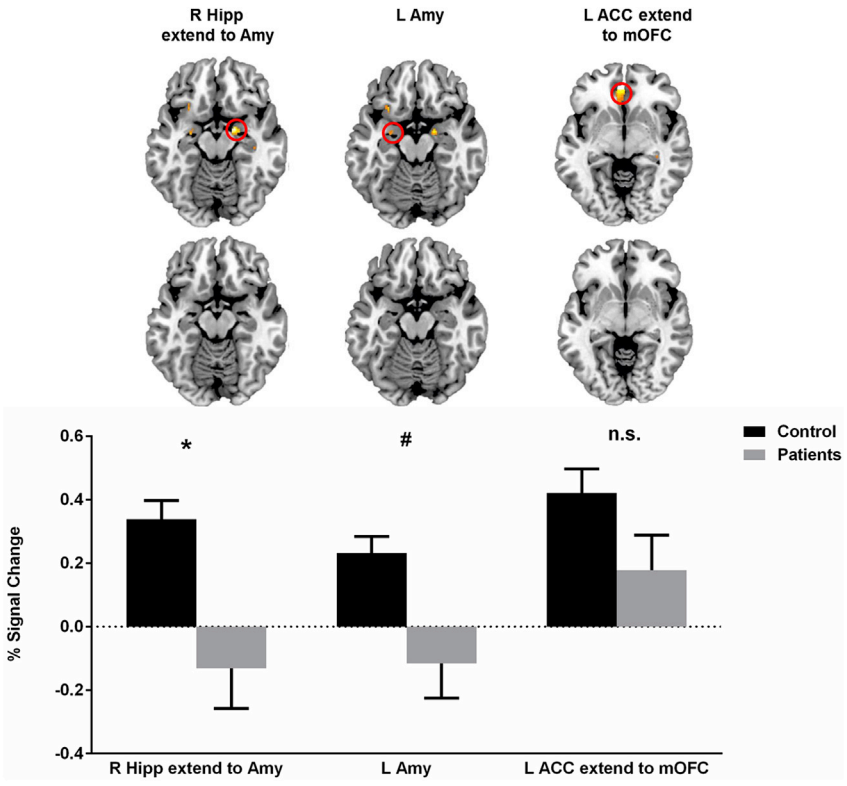

Fig. 3. Percentage of signal changes of the ROI regions in response to emotional and neutral pictures for healthy controls and for patients with olfactory loss. The error bars in the bar chart indicate the SEM. Bar chart showing between groups comparisons controlled for age, sex and depression severity (Beck depressions inventory score), *p < 0.05; #p < 0.1, n.s. non-significant. Activation is visualized on a template provided by MRIcron (www.nitrc.org/projects/mricron). The T-map threshold was set at $p_{uncorrected} \leq 0.001$ for visualization purpose. Hipp, hippocampus; Amy, amygdala; ACC, anterior cingulate cortex; mOFC, medial orbitofrontal cortex; L, left; R, right.

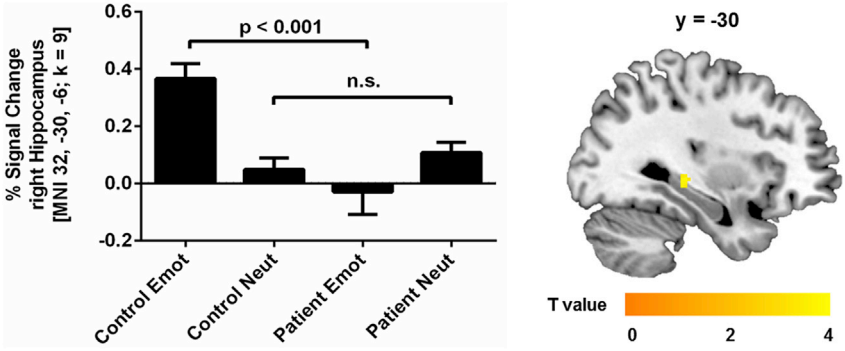

Fig. 4. Percentage of signal changes in the right hippocampus in response to emotional and neutral pictures separately for healthy controls and for patients with olfactory loss. The error bars indicate the SEM. Activation is visualized on a template provided by MRIcron (www.nitrc.org/projects/mricron). The T-map was threshold was set at $p_{uncorrected} \leq 0.001$ for visualization purpose. n.s. not significant.

overall human olfactory function (Buschhuter et al., 2008). The olfactory information projects from the OB to various brain structures including the piriform cortex, amygdala, entorhinal cortex, and from those first stations, the olfactory information is projected to the hippocampus and OFC (Gottfried, 2010). In the animal model, experimental olfactory bulbectomy (removing the olfactory bulb) is followed by a structural degeneration of hippocampus and amygdala (Carlsen et al., 1982) and accompanied by reduced activation in the frontal cortex, cingulate cortex and amygdala (Wrynn et al., 2000). The current finding suggests a similar mechanism for humans - the OB volume may modulate emotional responses through its functional link to the hippocampus and other limbic structures. In line with this reasoning, our data confirm the previously reported reduced OB volume in patients with olfactory disorders (Mueller et al., 2005). Such reduced OB volume may result in diminished synaptic input to the hippocampus and - in line with animal studies - potentially even to hippocampal degeneration. This may explain the dysfunction in emotion perception and processing in patients with olfactory disorders. An alternative explanation refers to proinflammatory cytokine which may cross the blood-brain barrier and inhibit neurogenesis within the hippocampus (Vallieres et al., 2002). This release of cytokines in response to infection occurs in some conditions causing olfactory loss, such as respiratory tract virus infection or sinonasal diseases (Noah et al., 1995; Rudack et al., 1998). However, the cross-sectional design of the current study makes it impossible to detect causal relationships. As the hippocampus and potentially also the OB undergo continuous neurogenesis (Eriksson et al., 1998; Duan et al., 2008; Huart et al., 2013; Lotsch et al., 2014), and as olfactory trainings among patients with olfactory loss leads to enhanced OB volume (Rombaux et al., 2006; Negoias et al., 2017), longitudinal studies may shed light on the question of whether emotional processing and hippocampal activity can be improved by olfactory training. Our own work indicates that olfactory training for the duration of three months in older participants can enhance mood (Wegener et al., 2018).

Besides the hippocampal dysfunction, attenuated brain response to

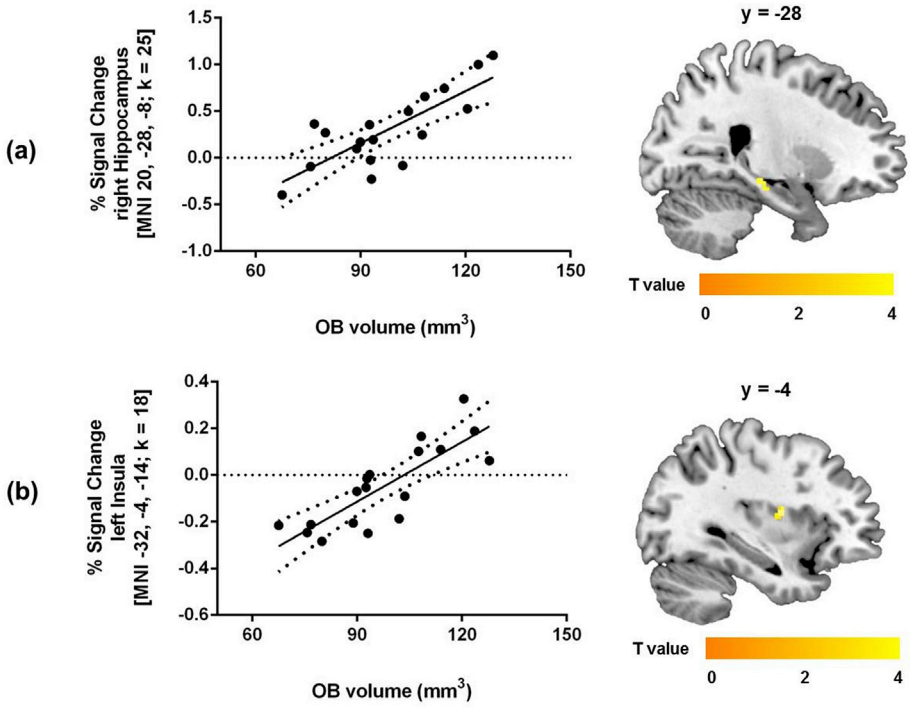

Fig. 5. Significant positive associations between the olfactory bulb (OB) volume and brain activation of the right hippocampus and left insula in response to emotional and neutral pictures in healthy controls. Scatter plots show the correlation between OB volume (in mm^3) and brain activation level (shown as percentage of signal changes) for right hippocampus (Pearson $r = 0.79$, $p < 0.001$) and left insula (Pearson $r = 0.82$, $p < 0.001$). Activation of significant cluster is visualized on a template provided by MRIcron (www.nitrc.org/projects/mricron). The T-map was threshold was set at $p_{uncorrected} \leq 0.001$ for visualization purpose.

emotion pictures was further detected in the amygdala. This was however not found in between-group comparisons or in the interaction effect. One plausible reason could be the experimental paradigm applied. The pictures from the IAPS may not be the most potent stimuli to elicit emotional responses in certain brain areas such as the amygdala, insula and ACC, as compared to emotional faces (Britton et al., 2006). In addition, unlike the amygdala and hippocampus which receive direct projections from the primary olfactory areas (Wilson et al., 2006), other emotional eloquent regions such as the ACC and insula maybe less affected by olfactory loss. The current study did not show the previously reported involvement of the piriform cortex in emotional picture processing. One possible explanation is that this area is more frequently engaged in cross-modal emotional processing following sensory-coupled emotional inductions (Satpute et al., 2015), such as the one introduced by Schulze et al. (2017) in which the emotional facial expressions were used as a primer for incoming olfactory stimuli.

Some limitations of the current study need to be addressed. The study was based on a well-defined group of patients with olfactory loss, however , this resulted in a rather small sample size, therefore the statistical power is reduced. In addition, patients had mixed causes for their olfactory loss with two patients having traumatic brain injury. To eliminate any interference by the brain injury, additional analyses were run excluding those two patients. The results stayed the same. Nevertheless, replication studies are necessary. In the same line of arguing, the different etiologies of olfactory loss most likely differ in their impact on OB volumes. The olfactory function of patients with olfactory loss due to sinonasal disease typically fluctuates and intermittent olfactory input is centrally processed. In line, OB volumes appear normal as compared to healthy controls (Han et al., 2017). Traumatic brain injury on the other side typically leads to the absence of olfactory information and significant OB volume reductions (Han et al., 2018). The differential reduction of OB volumes among patients with olfactory loss could explain the missing link between OB volumes and emotional brain responses, however, our sample size does not allow for such subgroup analyses.

In conclusion, the current study revealed that patients with olfactory loss have blunted hippocampal responses to visual emotional cues. In addition, there was a positive association between the OB volume and hippocampal or insular activation to emotional cues in healthy controls. These findings suggest a functional involvement of olfactory structures in emotional processing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2018.12.004.

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