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A Methodological Investigation of a Dental MRI Coil to Obtain Functional Signals from the Human Olfactory Bulb

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Abstract

Background: Mammalian olfaction begins with transduction in olfactory receptors, continues with extensive processing in the olfactory bulb, and culminates in cortical representation.

Most rodent studies on the functional neuroanatomy of olfaction have concentrated on the olfactory bulb, yet whether this structure is tuned only to basic chemical features of odorants or also to higher-order perceptual features is unclear.

New method: Whereas studies of the human brain can typically uncover involvement of higher-order feature extraction, this has not been possible in the case of the olfactory bulb, inaccessible to fMRI. The present study examined whether a novel method of acquisition using a facial coil could overcome this limitation.

Results: A series of experiments provided preliminary evidence of odor-driven responses in the human olfactory bulb, and found that these responses differed between individuals.

Comparison with existing methods and Conclusions: The present preliminary technical achievement renders possible to design novel human odor fMRI studies by considering the olfactory system from the olfactory bulb to associative areas.

Keywords

Olfactory bulb, human olfaction, fMRI method, perception

1. Introduction

Any environmental volatile molecules with certain properties (appropriate polarity, water solubility, vapor pressure, etc.) has a chance of being detected and discriminated by olfactory receptors in the nasal cavity. The cilia of sensory neurons are in direct contact with inhaled molecules, and contain olfactory receptors which bind to odorant molecules and initiate the neural message from the olfactory nerve to the olfactory bulb. Each olfactory cell expresses one of ~350 receptor proteins that recognize certain molecular features of the odorant; the axons of cells bearing the same receptor type converge on the same glomerulus, a functional unit in the olfactory bulb (OB) (Firestein, 2001; Secundo et al., 2014). The olfactory information is then transmitted to a network of primary and secondary areas in the temporal and frontal lobes: in ascending order, piriform cortex, amygdala, orbitofrontal cortex and insula (Gottfried, 2010; Yeshurun and Sobel, 2010).

In animals, most functional studies have focused on the olfactory bulb (Johnson and Leon, 2007; Mandairon and Linster, 2009). Whether this brain area represents only the basic chemical attributes of odorant molecules or also higher-order perceptual features remains an open question. One reason for this is that, whereas there are effective methods to explore OB functionality in mammals, access to perceptual experience is a limitation of animal models. Contrarily, asking humans about their conscious experience of smells is possible, but up to now there has been no effective way to measure activity in the human olfactory bulb, which is perhaps the most important structure in the olfactory system. Thus, the scientific interest of examining functionality in the human olfactory bulb is great. In contrast with the accessibility of primary and secondary areas through fMRI (Grabenhorst et al., 2007; Howard et al., 2009; Small et al., 2005), source localization of electroencephalography- (EEG -) event related potentials (Iannilli et al., 2015) or of human olfactory epithelium through electro-olfactograms (Lapid et al., 2011), the functionality of the human OB remains uninvestigated.

Its anatomy has been widely studied, but its small size limits in-vivo functional imaging exploration in humans. The main aim of the present study was therefore to set up a preliminary functional examination of the human OB using high-resolution fMRI. To achieve this aim, human OB functional activation was explored with fMRI using a dental MRI receiving surface coil in two different studies.

2. Materials and Methods

2.1. Participants. The participants were 14 volunteers (mean age \pm SD: 25.07 \pm 2.3 years; 6 female, 8 male) in the first study, and 13 volunteers (24.85 \pm 2.3 years; 5 female, 8 male) in the second. They received monetary compensation for the time spent in the laboratory. The recording procedure was explained in great detail to the volunteers, who provided written consent prior to participation. The study was conducted according to the Declaration of Helsinki and was approved by the institutional review board at the Medical Faculty of TU Dresden (n° EK110032014). Detailed medical history combined with ENT examination of the nasal cavity and odor perception assessment by the “Sniffin' Sticks” test (Hummel et al., 2007) ascertained that participants were in good health with normal sense of smell.

2.2. Odorants. Three different odorant molecules were used: (1) 1-butanol (“BUT” - CID 263: rancid-sweet odor), diluted in propylene glycol (PG) at 1.5% and 3%, (2) pure 2-phenylethyl alcohol (“PEA” - CID 6054: rose-like odor), and (3) p-menth-8-en-3-ol (“MEN”-CID 24585: minty odor), diluted in PG at 50%. Three odorant conditions were tested per study (Study 1: BUT-1.5%, BUT-3%, PEA; Study 2: BUT-3%, PEA, MEN-50%).

2.3. Experimental Protocol. Olfactory stimuli were administered using a computer-controlled olfactometer (Sommer et al., 2012), allowing application of rectangular-shaped stimuli with controlled stimulus onset, at an airflow of 1.45 ± 0.02 l/min; this rate of airflow, when humidified and presented at room temperature, does not produce irritation, nasal congestion or increased mucus discharge. A Teflon™ cannula directed the gaseous stimulus from the olfactometer, placed outside the MRI room, to the participant's nose.

In both studies, participants underwent two functional runs of 9 minutes each, including 6 “On/Off” blocks per odorant condition, for a total of 18 “On/Off” blocks per functional scan. During each “On” block (duration: 15 sec), the odorant was presented for 1s at 1s intervals. Odorless air replaced the odorant in the “Off” block (duration: 15 sec). Statistical analyses considered the entire “On” block (minus the first RT) as the “Odor” condition, and the entire “Off” block (minus the first RT) as the “Air” condition (see Statistical Analyses section).

In study 1, the stimulation site was in the right nostril. To further explore the possibility that respiration can modulate odor-evoked OB responses, two different breathing methods were used separately: only nasal breathing, or oral breathing using the velopharyngeal closure technique (Kobal, 1981) (breathing only through the mouth by lifting the soft palate), which participants were trained to use during the scan; this technique enables olfactory stimulation to be unaffected by patterns of inhalation and exhalation. In study 2, the stimulation site was alternately the right or the left nostril separately in the two functional runs, with the initial site selected randomly. Only breathing with the velopharyngeal closure technique was applied.

In both studies, nasal respiration was recorded throughout the functional sessions, using an airflow sensor (AWM720, Honeywell, France) connected to nasal cannulae positioned in each nostril (Fournel et al., 2017). The physiological signal was amplified and digitally recorded at 100 Hz using LabVIEW software®. Inspired air volume during “On” and “Off” blocks was calculated per participant per condition.

During the fMRI sessions, participants were not cued for any stimulus presentation or aware of the identity of the stimuli during the sessions. They were not asked to perform any tasks during stimulus presentation but, after each functional session, were asked to rate odorant pleasantness on a scale from -5 (very unpleasant) to +5 (very pleasant) and stimulus intensity, familiarity, coolness and irritation, on a scale from 0 (not at all intense, familiar, cool, irritating) to 10 (very intense, familiar, cool, irritating). Participants were also asked to freely describe the odorants by answering the question “What did you just smell?”, which gave information about their semantic experience of smells. **Supplementary Figure 1A and 1B** illustrates these perceptual data for both studies.

2.4. fMRI acquisition. The fMRI data were collected with an EPI spin-echo sequence (3 Tesla fMRI-scanner; Siemens Verio, Erlangen, Germany); 15 slices; matrix: 128x96; time to repetition (TR): 1,860ms; time to echo (TE): 36ms; flip angle: 90°; slice thickness: 2mm; EPI slice; voxel size: 2x0.80x0.80mm³; field of view: 102.4 x 76.8 mm²) (see **Figure 1A** for field of view). A high-resolution T2-weighted image was acquired (TR=4,730ms / TE=149ms; voxel size: 2x0.47x0.47mm³) and used to draw individual regions of interest (ROI) within the OB.

We used a prototype 4-channel receiving surface flex coil (Dental 4-Channel Coil; NORAS MRI Products GmbH, Höchberg, Germany) compatible with 3T Siemens MR Systems (weight: 0.8 kg; size: 15cm x 10cm x 10cm) previously developed for image acquisition in the maxillofacial area (in which the OB is located) (**Figure 1B**). To maximize signal-to-noise ratio (SNR), the surface coil was centered on the area of the OB (the coil increases the magnetic sensitivity by limiting the spatial area of reception). Anatomical SNR values within our area of interest (OB) ranged from 37.36 to 180.42 for Study 1 and from 50.09 to 108.92 for Study 2. For temporal SNR (tSNR), maximum values ranged from 2.67 to 12.34 for Study

1 and from 2.09 to 12.60 for Study 2. Expected tSNR values in brain grey matter at 3T for a spatial resolution of 1x1x3 mm are around 20 (Triantafyllou et al., 2005); in the present case, tSNR could be expected to be lower, since the spatial resolution was lower (0.8x0.8x2 mm). Moreover, our region of interest was located in the ventral part of the brain, where tSNR is expected to be lower (Aquino et al., 2019). Due to the non-homogeneous B1-distribution, the coil was only used as receiver, the transmitting coil being the built-in body coil of the scanner. Furthermore, for safety reasons (no active decoupling) the built-in spine coils were completely dismantled before measurements. The coil was flexible and easy to bend to match the convexity of the frontal scalp, and was kept in position by a Velcro strip. The participant was asked to keep their eyes closed throughout functional acquisition. Further information about the coil can be found at <http://www.noras.de/en/mri-products/dental-4-ch-coil/>.

Figure 1 here

2.5. Statistical analysis. To first ensure the presence of a BOLD signal within the OB, signal intensity in this area was estimated at individual level using two criteria: 1/ presence of potential distortions, and 2/ quality of co-registration between the T2 anatomical image and the functional EPI image. To this end, for each participant, two separate ROIs of the left and right OB were drawn on the T2- anatomical image, and were then projected onto the EPI images. This analysis revealed that, whereas some participants exhibited BOLD signal within the anatomical ROIs (see for instance “sub-02” in **Figure 2A** for Study 1 and “sub-07” in **Figure 4A** for Study 2), for other participants the signal was absent (e.g. “sub-16” in **Figure 2A** for Study 1 and “sub-12” in **Figure 4A** for Study 2).

To decide the participant’s inclusion in the main statistical analyses, we then compared signal intensity within the OB in the mean EPI of each participant. To this end, the general

distribution of signal intensity was computed for all ROIs and all participants. This analysis revealed that the total range of BOLD signal intensity was between 0 and 15,000 units voxel intensity. **Figures 2B and 4B** depict these distributions for each individual. It can be seen that, while for some participants signal intensity was above the first quartile of the distribution (Q1: 1,594.975; which can be considered as a noisy area; pink rectangle in **Figures 2B and 4B**), for others a large proportion of the data fell within Q1. Only participants with at least 65% of data above Q1 were used in the statistical analyses: i.e., 10 of the 14 participants in Study 1 and 7 of the 13 participants in Study 2 were included. To better understand which factors may contribute to discriminate included vs. non-included participants, we compared these two groups along 3 variables, namely, size of the OB (in voxels), SNR and tSNR. In study 1, whereas no differences were observed for OB size (included (*mean*+*SEM*): 152.450+/-9.682 ; non-included: 204.600+/-39.205 ; Z=-1.148, p=0.125) and SNR (included: 100.508+/-9.116 ; non-included: 81.973+/-25.225 ; Z =-1.438, p=0.075), included participants exhibited a higher tSNR than non-included participants (included: 2.620+/-0.346 ; non-included: 1.153+/-0.345 ; Z=-2.068, p=0.019). In study 2, no differences were observed between the two groups for OB size (included: 137.071+/-17.056 ; non-included: 169.167+/-36.723 ; Z<0.001, p>0.999) and SNR (included: 80.207+/-5.175 ; non-included: 79.830+/-8.612 ; Z=0.069, p=0.945). Although a greater tSNR was observed for included vs. non-included participants, this difference did not reach significance (included: 2.298+/-0.512 ; non-included: 1.323+/-0.272 ; Z=-1.091, p=0.137). Whereas these complementary analyses should be taken with caution because of small sample size, they tend to suggest that the current distinction between included and non-included participants depend more on functional signal than on anatomical data.

Statistical analysis then comprised two steps. First, to examine odor-induced activity in the OB and other areas included in the field of view, we performed a standard GLM analysis. To

optimize the BOLD signal, the study included the anterior part of the brain, and therefore the group analysis could not provide standardized coordinates as in conventional analysis; moreover, even if MNI coordinates could have been generated, there is currently no anatomical template for the human olfactory bulb. Thus, the group analysis could not properly delineate the functional activation of the olfactory bulb on the one hand and neighboring regions on the other. Therefore, as a second step, the group analysis was completed by ROI analysis, comparing summated activity within the olfactory bulb during the odorized (“Odor” condition) and non-odorized trials (“Air” condition).

The group analysis consisted firstly in creating a study-specific template, using the following steps : (i) first, brain matter was extracted from all T2 images by removing non-brain matter (skull, eyes, neck); (ii) second, the most representative T2 image was selected among all participants, to be used as initial reference (this was done separately for study 1 and study 2); (iii) third, the brains of all participants were registered to this initial reference (geometrical transformation performed with FLIRT software, FSL library, an automated algorithm for linear intra- and inter-individual brain image registration); (iv) fourth, output-registered images from the previous steps were averaged to create the final template used as a normalization space for group analysis. Preprocessing included motion correction, slice timing, anatomical segmentation (to compute both white matter and CSF masks), respiration signal down-sampling, smoothing with a $2 \times 2 \times 5$ mm FWHM kernel, and normalization to the created final template. Statistical analyses included subject-level analysis of Odor vs. Air conditions, using SPM 12 software. At group-level, independent one-sample voxel-wise t-tests were performed using Randomise software (FSL library).

The ROI analysis started with the creation of two separate ROIs, one in each hemisphere. These left and right ROIs were drawn on the high-resolution T2- anatomical image (mean VOI dimension: 135 voxels; volume: $64.79 \pm 24.43\text{mm}^3$; length: $10.97 \pm 1.90\text{mm}$). The

anatomical ROIs were then projected onto the functional EPI images. Using the same pre-processing steps as those used in the group analysis (but omitting smoothing and normalization steps), functional data were then analyzed. Here, for each participant and condition (“Odor” and “Air”), the OB activity at each data-point of the time-series functional signal was averaged (time window: from 1.88s to 14.88s). The block-averaged voxel-wise data points for all participants and conditions (“Odor” and “Air”) were then included in the analysis. Since sample size was small in both studies, a non-parametric test (two-tailed Wilcoxon signed-ranks) was used to assess whether the population mean ranks differed between the two paired conditions.

For both group and ROI analyses, white matter and CSF masks were used to estimate physiological artifacts by the *aCompCor* method (Behzadi et al., 2007). To ensure that white matter and CSF mask corrections do not include any OB voxels, OB ROI voxels were set to zero in the CSF and white matter binary masks. The following signals were included as regressors of no interest in first-level analysis: first 6 *aCompCor* components, 6 motion parameters, frame displacements, nasal breathing, with a discrete cosine transform basis set acting as high-pass filter (with 128s cutoff). For breathing correction, we first down-sampled the respiratory signal (256Hz) into the fMRI frequency (1/RT) using the Fourier method implemented in the “resample” Function on Scipy software (Python Library). Secondly, the down-sampled signal was used as co-variate in the further statistical analyses.

3. Results

3.1. Study 1. Inter-individual heterogeneity in odor-induced activity in the human OB

The standard GLM group analysis revealed significant activity in the area of the OB (p-value range: from 0.05 to 0.004) accompanied by significant BOLD responses in different parts of

the orbitofrontal cortex (from lateral to more medial areas) and in the anterior cingulate gyrus (p-value range: from 0.05 to 0.001) (**Figure 2C**).

Figure 2 here

We next examined odor-induced BOLD activity on ROI analysis. **Figure 2D** illustrates the time course of BOLD activity for respectively the contralateral (left) and ipsilateral (right) OB for Odors (green lines) and Air (red lines) (**Supplementary Figure 2** shows individual time-series for Study 1). **Figure 2E** depicts percentage signal change in the Odor (ON, green bars) and Air condition (OFF, red bars). Statistical analysis revealed no significant effect of odorant stimulation in the ipsilateral ($Z=-0.596$, $p=0.275$) or contralateral OB ($Z=0.142$, $p=0.556$). Note that no significant difference was observed between the Air condition (OFF) of the ipsilateral vs. contralateral mode of stimulation ($Z=-0.731$, $p=0.232$). Moreover, there was wide variation between individuals in odor-induced OB BOLD activity: (i) for the ipsilateral OB, 70% (7 out 10) of individuals showed greater activation for odors than for air and 30% showed the opposite; (ii) for the contralateral OB, 50% (5 out 10) of individuals showed greater activation for odors than for air and 50% showed the opposite (**Figure 2F, 1G**). We then analyzed whether respiration mode played a confounding role, by considering the two respiratory modes (nasal and velopharyngeal) separately. The analysis revealed: (i) for nasal respiration, no significant difference in ipsilateral ($z=0.318$, $p=0.625$) or contralateral OB activity ($z=-1.518$, $p=0.064$) between the odor and no-odor conditions (**Figure 3A**), and no significant difference between the no-odor conditions of the ipsilateral vs. contralateral mode of stimulation ($Z=-0.865$, $p=0.193$); (ii) for velopharyngeal closure respiration, no significant increase in OB activity in the right ($z=-$ and were observed in the left OB ($z=-0.461$, $p=0.322$, for both analyses) (**Figure 3B**). Finally, ROI analysis found no significant

effect of breathing mode on odor-induced OB BOLD activity. However, time-series analysis according to respiratory mode suggested that velopharyngeal respiration leads to a more reliable signal than nasal respiration (**Figures 3C and 3D**). Velopharyngeal respiration was associated with a more standard hemodynamic response, a fairly stable baseline for the Air condition, and a peak of activity a few seconds after odor onset in the Odor condition. In the light of this, only the velopharyngeal respiration mode was used in the second study, which made it possible to double the number of stimulations and therefore increase statistical power for a single mode of respiration.

Figure 3 here

3.2. Study 2. Replicating odor-induced activity in the human OB

Group analysis replicated the results of Study 1, showing significant activity in the OB region (p-value range: from 0.05 to 0.008). As in Study 1, additional significant BOLD responses were observed in the anterior cingulate gyrus and various parts of the orbitofrontal cortex (p-value range: from 0.05 to 0.001) (**Figure 4C**). Conventionally, group analyses are generally conducted using larger sample sizes in fMRI studies than in the present study (10 in Study 1 and 7 in Study 2); nevertheless, we obtained significant uncorrected p-values, comparable to a series of reports showing odor-induced activation in primary and secondary olfactory areas that are more easily accessible to fMRI (Bensafi et al., 2008; Boyle et al., 2009; Croy et al., 2010; Gottfried et al., 2004; Gottfried and Dolan, 2003; Rolls et al., 2010; Royet et al., 2011; Savic et al., 2009; Small et al., 2005).

Figure 4 here

The time courses of BOLD activity in the contralateral and ipsilateral OB in response to odors (green lines) and air (red lines) are depicted in **Figure 4D (Supplementary Figure 2** illustrates individual time-series for Study 2). Visual inspection of the curves revealed a hemodynamic response in the Odor condition in both ipsilateral and contralateral OB. The baseline Air condition was much more stable than in Study 1. **Figure 4E** illustrates mean signal changes in the Odor (ON, green bars) and Air condition (OFF, red bars). Results revealed a significant effect of Odor in the ipsilateral OB ($Z=-1.675$, $p=0.046$) but not the contralateral OB ($Z=-1.009$, $p=0.156$). On a descriptive level: (i) 85% (6 out of 7) of participants showed larger BOLD signal for odors than for air while 15% showed the opposite in the ipsilateral OB, and (ii) 71% (5 out of 7) and 29% respectively in the contralateral OB (**Figure 4F, 4G**).

4. Discussion

The olfactory bulb (OB), a small region located between the olfactory receptor layer and the piriform cortex, plays a key role in olfactory processing. Hitherto, functional exploration of this area was restricted to animal models such as rodents, dogs and monkeys. Functional study of the human OB is limited for a number of reasons, as discussed above. The present study sought to ask this issue so as to examine whether BOLD response to odorant stimuli can be measured in the human OB.

BOLD signal in the OB in response to odorant molecules has been widely documented in rats using MRI at 7T to 9.4T, with in-plane resolution ranging from 0.110 by 0.110 mm² to 0.390 by 0.390 mm² (Kida et al., 2002; Li et al., 2014; Martin et al., 2007; Murphy et al., 2016; Poplawsky and Kim, 2014; Sanganahalli et al., 2016; Schafer et al., 2006, 2005; Yang et al., 1998; Zhao et al., 2016). At similar magnetic field strengths (from 7T to 11.7T) and similar spatial resolution (0.100 by 0.100 mm²), fMRI activity was also examined in mice,

showing different response profiles according to odorant (Muir et al., 2019; Xu et al., 2005, 2003). As in the present study, other species were explored at low magnetic field and lower in-plane resolution. For instance, BOLD signal in response to smells were observed in dogs at 3T and in-plane spatial resolution of 3 mm² (Berns et al., 2015; Jia et al., 2014)). In monkeys, Zhao and colleagues (Zhao et al., 2015) observed a significant BOLD signal in the OB in response to smells at 3T with spatial resolution of 1.900x1.900 mm³. In humans, previous functional MRI studies of olfaction did not focus on the OB, but showed that areas involved in odor processing mainly comprise the piriform cortex (Fournel et al., 2016; Howard et al., 2009), amygdala (Anderson et al., 2003; Winston et al., 2005), orbitofrontal cortex (Bensafi et al., 2014; Gottfried et al., 2002b; Rolls et al., 2003), insular cortex (Bensafi et al., 2007; Wicker et al., 2003), cerebellum (Ferdon and Murphy, 2003; Sobel et al., 1998) as well as other areas such as the thalamus (Plailly et al., 2008; Sela et al., 2009; Tham et al., 2009) and hypothalamus (Savic et al., 2001). Activation in these areas is modulated by habituation (Poellinger et al., 2001; Sobel et al., 2000), and by odorant characteristics such as pleasantness (Anderson et al., 2003; Gottfried et al., 2002a; Rolls et al., 2003), or intensity (Anderson et al., 2003; Bensafi et al., 2008). However, one important piece missing from this complex functional puzzle is the OB. Most of the knowledge acquired in recent years about the human OB concerns histology, anatomy and plasticity (Lötsch et al., 2014; Maresh et al., 2008; Mazal et al., 2016). As mentioned above, functional imaging of the human OB has been limited because of the small size of this structure but also because it is located near the sinuses, which are a source of large artifacts in MRI, especially with high magnetic field strength.

In the present study, using a flexible surface (dental) receiver MRI-coil set-up, a 3 Tesla scanner with in-plane functional resolution of 0.800x0.800 mm² (lower than in rodent fMRI exploration, but higher than in dogs or monkeys), we obtained preliminary evidence of

a BOLD signal in response to odorant molecules in the human OB. In a first study, we showed that the BOLD signal within the OB was not constant between individuals: indeed, for some participants the signal was absent. Considering only participants for whom a signal was present, group analysis revealed significant activity in the area of the OB. However, region-of-interest analysis focusing on the entire anatomic volume of the OB did not reveal a significant difference between olfactory and non-olfactory conditions. Nevertheless, a descriptive analysis of the data revealed that the shape of the hemodynamic signal was more reliable when participants breathed only through their mouth (by lifting the soft palate) compared to nasal breathing. Thus, only oral respiration was used in the second study, which made it possible to double the number of stimulations (for the same respiration mode) and thus increase statistical power.

Like in the first study, the second study revealed that some participants did not exhibit any BOLD signal within the OB. On the other hand, for those for whom a signal was present, both the group analysis and the ROI analysis revealed significant BOLD activity in the OB in response to olfactory stimuli. Interestingly, considering time-course in this second study, the Odor condition induced a sustained positive signal with a peak at 3 to 5 seconds, as typically observed in fMRI block designs (Buxton et al., 2004). In contrast, the control Air condition induced a more or less stable signal with a mixture of positive and negative values. Negative BOLD signal effects are commonly called brain deactivations and are linked in the literature to methodological issues (e.g., how active and control tasks are modeled in the image-analysis strategy), as well as to a real decrease in neuronal activity (Gusnard et al., 2001; Shulman et al., 1997). In the present study, however, negative signals were always accompanied by positive signals within the same time-series, excluding the possibility that such effects were due to methodological issues.

The present preliminary technical achievement makes it possible to design novel studies in the field of olfactory perception by setting up new experiments to shed further light on the content of odor representations within the OB. Are these representations of purely chemical types? Or do they have a perceptual-like nature? If so, what are the respective weights of hedonics and perceptual quality in organizing these representations? These issues, previously addressed in animals, remain unexplored in humans. Abundant animal data show the existence of chemical-type representations in the OB (Johnson and Leon, 2007), and the hypothesis of perceptual/emotional representation of odors is also present in the animal literature. Previous investigations in rodents showed that odors inducing different behavioral responses induced specific representations in the OB. Using optogenetic manipulation in freely behaving mice paired with immediate early gene mapping, Kermen and colleagues (Kermen et al., 2016) showed that odors associated with withdrawal behavior induced greater activity in the posterior part of the OB, whereas odors evoking approach behavior induced greater activity in the anterior part. Studies in insects showed that total neural response in the olfactory system reflected odor attraction behavior in larval *Drosophila* (Kreher et al., 2008), a finding that was extended to other species, including mice and rats (Haddad et al., 2010). In the present study, the small number of odorants used in the design precluded testing these hypotheses; a larger set of stimuli would enhance chemical, perceptual and hedonic diversity across stimuli and participants and could shed light on these important issues in humans.

A limitation of our work may relate to the use of only mono-rhinal odorant stimulation because this may reduce the intensity of the brain response. Intuitively, stimulating both nostrils should correspond to greater activation of the OB with respect to the stimulation of only one. However, the literature in the field is not as rich as one might think. The only work that explicitly compares the two methods of odorant delivery during an fMRI experiment observes that “mono-rhinal and bi-rhinal stimulation seems to elicit approximately the same

activity pattern “ (Zatorre and Jones-Gotman, 2000). Animal studies suggest a similar take. For example, Slotnick and colleagues (Slotnick and Schoonover, 1984) studying the olfactory threshold in bulbectomized rats observed that “there is no increase of sensitivity threshold” in this group compared with a group of rats with two bulbs, not supporting the idea of central summation of the bi-rhinal inhaled odorants. Our thought is that the topic is both methodologically and ecologically important, since natural olfaction involves both nostrils, and should be further addressed in future studies.

In conclusion, whereas our methodological approach needs to be improved both at the experimental level (e.g. by adding more stimuli and more participants), and fMRI measures (by developing new coils more adapted to measure BOLD signal in ventral areas), our findings should be seen in the perspective of a better understanding of the neural mechanisms underlying human olfaction: collecting perceptual data in humans and relating these, in the same participants, to functional recordings along the olfactory system from the olfactory bulb to associative areas will disclose the organization of this chemosensory system. At system level, our findings will help in understanding how the different features of smells are encoded in the olfactory system, including its first relay area. Finally, the present findings may have broad and important implications both for the field of olfaction and for other neuroscientific questions involving the study of small high-susceptibility structures.

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Declaration of Interests

None. The authors declare no competing interests.

Figure Legends

Figure 1. (A) Field of view of the fMRI acquisition (102.4 x 76.8 mm² / 15 slices) (B) Surface flexible coil.

Figure 2. Study 1. A) Anatomical T2 and EPI coronal view centered on olfactory Bulb for two different participants. Red contours depict the location of the olfactory bulb in both the anatomical and the EPI images. Whereas for Sub-02, a BOLD signal is observed in the OB, this is not the case for sub-16. B) BOLD signal intensity distribution in the human OB for each participant. The pink rectangle depicts the first quartile of the distribution. C) Coronal view of the group-analysis showing significant activation in the OB (Olfactory bulb) and in other frontal areas. D) Time course of BOLD activity respectively for the contralateral OB and the ipsilateral OB for odors (green lines) and air (red lines) (black bars corresponds to 1-sec Odor pulse in the Odor condition or 1-sec Air pulse in the Air condition). E) Contralateral and Ipsilateral OB response to right nostril stimulation displayed as box plot for the Odor (ON, green bars) and the Air (OFF, red bars) conditions. F) Individual BOLD response to the Odor (ON) and Air (OFF) conditions in both the contralateral (upper panel) and the ipsilateral (lower panel) conditions. G) BOLD signal in the OB at the individual level for odor (x-axis) and air (y-axis) conditions respectively for the contralateral OB and the ipsilateral OB.

Figure 3. Odor-induced activity in the OB as a function of respiration mode. (a) Nasal respiration. (i) Box plot: Odors (in green) vs. air stimulation (in yellow) induced no significant difference neither in the left OB nor in the right OB. (ii) and (iii) depict OB activation at the individual level for odor (x-axis) and air (y-axis) conditions respectively for the left OB and the right OB. (b) Velopharyngeal closure. (i) Box plot: The ipsilateral (right) OB response to the odorant was significantly greater than that observed for the control air condition (**: $p=0.0035$). (ii) and (iii) depict OB activation at the individual level for odor (x-axis) and air (y-axis) conditions respectively for the left OB and the right OB. Each dot corresponds to the summed activity (SA).

Figure 4. Study 2. A) Anatomical T2 and EPI coronal view centered on olfactory Bulb for two different participants. Red contours depict the location of the olfactory bulb in both the anatomical and the EPI images. Whereas for Sub-07, a BOLD signal is observed in the OB, this is not the case for sub-12. B) BOLD signal intensity distribution in the human OB for each participant. The pink rectangle depicts the first quartile of the distribution. C) Coronal view of the group-analysis showing significant activation in the OB (Olfactory bulb) and in other frontal areas. D) Time course of BOLD activity respectively for the contralateral OB and the ipsilateral OB for odors (green lines) and air (red lines) (black bars corresponds to 1-sec Odor pulse in the Odor condition or 1-sec Air pulse in the Air condition). E) Contralateral and Ipsilateral OB response to right nostril stimulation displayed as box plot for the Odor (ON, green bars) and the Air (OFF, red bars) conditions. F) Individual BOLD response to the Odor (ON) and Air (OFF) conditions in both the contralateral (upper panel) and the ipsilateral (lower panel) conditions. G) BOLD signal in the OB at the individual level for odor (x-axis) and air (y-axis) conditions respectively for the contralateral OB and the ipsilateral OB.

Supplementary Figure 01. Principal component analysis showing two-dimensional representational spaces of odors in Study 1 (A) and Study 2 (B) based on perceptual ratings (dark grey: 1-butanol 3%, light grey: 1-butanol 1.5%, green: p-Menth-8-en-3-ol; violet: 2 phenylethyl alcohol). Each colored dot corresponds to the odor barycenter in the PCA space and is accompanied by both a 3D molecular structure of the odorant and a word-cloud of semantic descriptions.

Supplementary Figure 02. Individual time-series for Study 01 and Study 02.

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