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No Effects of Handedness on Passive Processing of Olfactory Stimuli: An FMRI Study

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Abstract The study aimed to investigate possible differences in lateralized olfactory processing in left- and right-handed subjects using a functional MRI paradigm. Twenty-four (14 female, 10 male) right-handers and 24 (14 female, 10 male) left-handers participated; their mean age was 24.0 years, all were in excellent health with no indication of any major nasal or other health problems. The rose-like odor phenyl ethyl alcohol and the smell of rotten eggs (H_2S) were used for relatively specific olfactory activation in a block design using a 1.5-T MR scanner. Results indicated no major differences in lateralized olfactory activation between left- and right-handers. This suggests that in simple olfactory tasks, handedness does not seem to play a substantial role in the processing of olfactory information.

Keywords Olfaction · Smell · Hemisphere · Lateralization

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Introduction

Olfactory stimuli are processed to some degree ipsilaterally to the stimulated nostril which is different from other sensory systems (Doty et al. 1997; Lascano et al. 2010). However, similar to other systems, effects of handedness should be expected (Bryden and Steenhuis 1991).

Lateralized differences in olfactory sensitivity in relation to the subjects' handedness have been reported in a number of psychophysical experiments. Frye et al. (1992) showed for 2-butanone odor detection thresholds that right-handers (RH; $n=37$) were slightly more sensitive on the left side of the nose, whereas left-handers (LH; $n=38$) were more sensitive on the right side. However, other research showed the contrary (Youngentoub et al. 1982), with LH being more sensitive on the left side whereas RH ($n=10$) had lower n-butanol odor thresholds on the right side. Two other studies did not find differences for phenyl ethyl alcohol (PEA) detection thresholds between LH and RH (Betchen and Doty 1998; Zatorre and Jones-Gotman 1990).

When investigating more demanding olfactory tasks, Zatorre and Jones-Gotman (1990) reported that, other than with detection thresholds, odors are in general better discriminated when presented to the right nostril, this phenomenon being not significantly influenced by the subjects' handedness. In contrast, Hummel et al. (1998) reported the presence of such an influence.

The current study aimed to investigate effects of handedness on functional odor processing in order to clarify the role of handedness in olfaction. Using a functional magnetic resonance imaging (fMRI) paradigm allowed us to regard differences between LH and RH in olfaction at the most basic level, independently of olfactory performance. Preliminary work by Yousem and co-workers, who studied responses from 16 RH and 3 LH subjects, showed striking differences with regard to the right orbitofrontal cortex (stronger activation in RH) and the left anterior insular cortex (stronger activation in LH). However, this pilot study appeared to be statistically underpowered in the group of LH to provide reliable results. Another study by Royet et al. (2003) investigated handedness-related differences between 14 LH and 14 RH subjects. In this experiment, focusing on valence-related processing of odors, the authors found more right-sided activation in the insula in LH compared to more left-sided activation of the insula in RH.

In the current experiment, we set out again to address the question of handedness on the processing of olfactory information in a large group of young, healthy subjects. Importantly and different from previous work by Royet and colleagues, participants during the entire experiment had no specific task during odor presentation other than passive smelling. The simple expectation was that activation in olfactory-eloquent areas would be identical but mirrored in RH and LH subjects, that is RH subjects should show lateralized responses opposite to those shown by LH subjects.

Methods

Participants

Fourty-eight participants were recruited for the current study, including 24 (14 female) RH and 24 (14 female) LH participants (as assessed via the Edinburgh Handedness Inventory, Oldfield 1971). None of these participants reported a history of chronic medication; of neurological, psychiatric, endocrine, or immunological diseases; or diseases related to the upper respiratory tract. Participants had a mean age of 24.0 years (SD=4.3, range 18–45 years); LH (M=24.3, SD=5.0 years) and RH (M=23.8, SD=3.5 years) did not differ in age [$t(46)=0.369$, $p>0.25$]. Using the "Sniffin' Sticks" test kit (Hummel et al. 1997, 2007), normal olfactory function was verified in all participants.

Stimulus Presentation

Participants underwent four consecutive sessions. Within two of these sessions PEA (40 % *v*/*v*) was presented, within the other two H_2S (4 ppm) was presented. Each odor was presented unilaterally to the left nostril in one session and to the right nostril during the other session, with subjects knowing which nostril was going to be stimulated. This information was provided in order to prevent the participants from concentrating on finding out which side the odors were presented to. The order of sessions was randomized across participants. During each of six on blocks in one session (see fMRI protocol and analysis), seven stimuli were presented, resulting in a total of 42 stimuli in one session. Each on block was followed by a resting period of 20 s without stimulation. Odors were presented intranasally (inner diameter of the Teflon™ tubing, 4 mm) using a computer-controlled olfactometer (OM6b; Burghart, Wedel, Germany). In order to avoid any mechanical stimulation, odor pulses were embedded in a constant flow of humidified, odorless air. Total air flow was 6 l per min/nostril. During the on period, stimulus pulses lasted 1 s, the interval between stimuli was 2 s. During each of the scanning sessions, participants had no task other than passively smelling the odors.

Odor Ratings

During short breaks following each session, participants rated the odor's intensity (0=extremely low intensity, 10=extremely high intensity) and hedonic quality (−5=extremely unpleasant, 5=extremely pleasant) and indicated the side at which they had perceived the odor (−5=definitely left side, 5=definitely right side).

fMRI Protocol and Data Analysis

We used a 1.5-T scanner (SONATA-MR; Siemens, Erlangen, Germany) for fMRI data acquisition. For functional data 96 volumes per session were acquired by means of a 26 axial slice matrix 2D SE/EP sequence (TR 2,500 ms/TE 40 ms, matrix 64×64, voxel size $3\times3\times3.75$ mm^3). In each session the participants received eight scans during the 20-s on block and eight during the 20-s off block. On and off blocks were repeated six times, and each session lasted 4 min. Additionally, T1-weighted images were acquired using a 3D IR/GR sequence (TR 2,180 ms/TE 3.39 ms) to localize activated areas. Due to technical problems, data of four participants (all RH) had to be excluded from analysis, resulting in a total sample size of $n=44$.

Preprocessing and statistical analysis were performed using the statistical parametric mapping software package (SPM8; Wellcome Trust Centre for Neuroimaging, London; www.fil.ion.ucl.ac.uk/spm) implemented in Matlab R2010b (Math Works Inc., Natick, MA, USA). Head motions across time were corrected by realigning all scans to the first volume. Participants' T1-weighted images were co-registered to the corresponding mean EPI images and subsequently normalized to Montreal Neurological Institute (MNI) standard space using the segmentation procedure. EPI images were then normalized using the parameters written during segmentation of co-registered T1-weighted images and spatially smoothed using an isotropic Gaussian kernel at 9 mm full width at half maximum. Coordinates of the activation are presented according to MNI. Analysis was based on *t* tests with a cluster level of 16 and $p<0.05$ (FWE corrected). In order to test our hypothesis of differences in activation between RH and LH participants in olfactory processing areas, we performed a small volume correction using masks for primary (amygdala, piriform cortex, entorhinal cortex), and secondary (orbitofrontal cortex, insula, hippocampus, thalamus, hypothalamus) olfactory areas. Masks were created using the WFU PickAtlas 3.0.3 software (Maldjian et al. 2004).

Ratings were analyzed using a three-way ANOVA including the between subject factor "group" (RH vs. LH), and two within subject factors, "side" and "odor," where "side" refers to the nostril tested (left, right) and "odor" refers to the odor presented (PEA, H_2S). Subsequently, nested effects were isolated and calculated in accordance with Page et al. (2003).

Results

Odor Ratings

Analysis revealed a significant main effect of "odor" on both pleasantness and intensity ratings. Participants judged PEA to be more pleasant [main effect "odor"—$F(1, 42)=125.1$, $p<0.001$, $f=0.749$, power=1.000] and less intense [main effect "odor"—$F(1, 42)=13.6$, $p=0.001$, $f=0.245$, power=0.950] than H_2S, which in fact was rated as unpleasant (see Fig. 1). No significant main effects or interactions concerning intensity and pleasantness ratings involving either "group" or "side" were observed.

Results further show, as indicated by a main effect of "side," that on average participants correctly indicated "right side" when odors were presented to the right nostril and "left side" when odors were presented to the left nostril [main effect "side"—$F(1, 42)=93.86$, $p<0.001$, $f=0.691$, power=1.000]. Nested effects analysis of a significant "odor" by "side" interaction ["odor" by "side"—$F(1, 42)=14.02$, $p=0.001$, $f=0.250$, power=0.955, see Fig. 2] revealed that participants were even more confident when presented with H_2S [nested effects: "side" within H_2S—$F(1, 42)=144.10$, $p<0.001$] than with PEA [nested effects: "side" within PEA—$F(1, 42)=22.64$, $p<0.001$]. No further main effects or interactions were observed.

Main Effect of "Odor"

Focusing on the aspects of olfactory processing, an analysis of the main contrast of on (odor) vs. off conditions was conducted. Significantly enhanced activation in areas known to be involved in olfactory processing was evident (see Fig. 3), especially with respect to secondary olfactory areas like the orbitofrontal cortex and the insula (for details, see Table 1).

Comparison Between the Groups for Both Presentation Sides

Comparison of the on contrasts of the RH group with the on contrasts of the LH group revealed no suprathreshold voxels within the primary or secondary olfactory processing areas, neither when regarded for both presentation sides simultaneously, nor when left- and right-sided stimulation were regarded separately. An additionally performed whole brain analysis did not show activation differences in areas other than those related to olfactory processing.

Comparison Between Presentation Sides for Both Groups

Comparing the on contrasts during right-sided stimulation with the on contrasts during left-sided stimulation did not show any suprathreshold voxels within primary or secondary olfactory processing areas, neither for the whole samples nor when RH and LR groups were regarded separately. An additionally performed whole brain analysis did not show activation differences in areas other than those related to olfactory processing.

Discussion

The present results obtained in a large sample indicate that handedness plays no major role in the passive processing of olfactory information. This provides a hypothesis for explaining the somewhat confusing literature on handedness-related

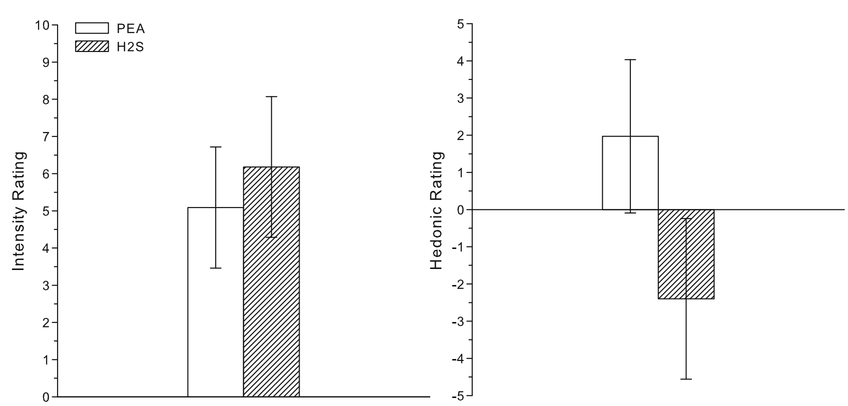

Fig. 1 Hedonic and intensity ratings (means, standard deviations) for PEA and H_2S. Higher ratings refer to greater perceived pleasantness and/or intensity. For pleasantness ratings *negative numbers* indicate unpleasant sensations, *positive numbers* indicate pleasant sensations

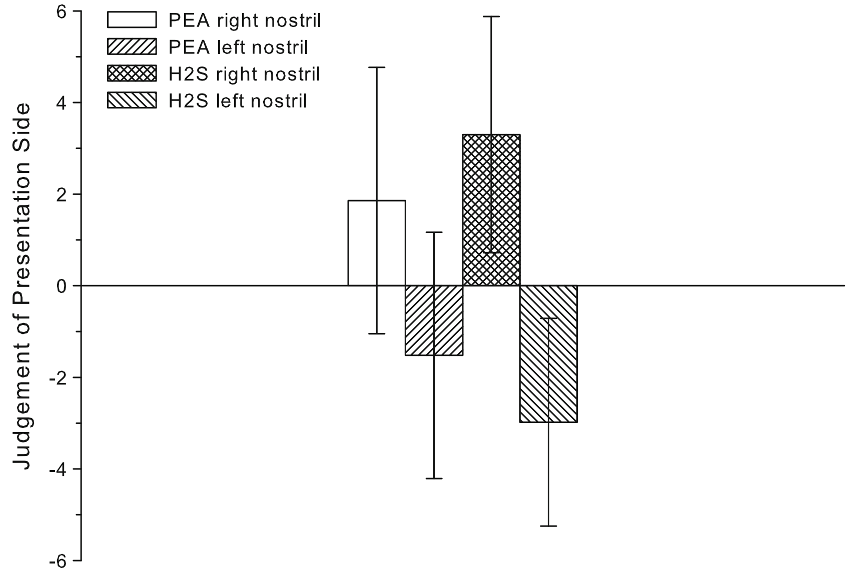

Fig. 2 Indications of the presentation side for left- and right-sided presentations of PEA and H_2S. Ratings >0 refer to an indication of right-sided stimulation, ratings <0 refer to an indication of left-sided stimulation

differences in olfaction, as the reported effects seem to vary with the relative demand of the respective olfactory tasks.

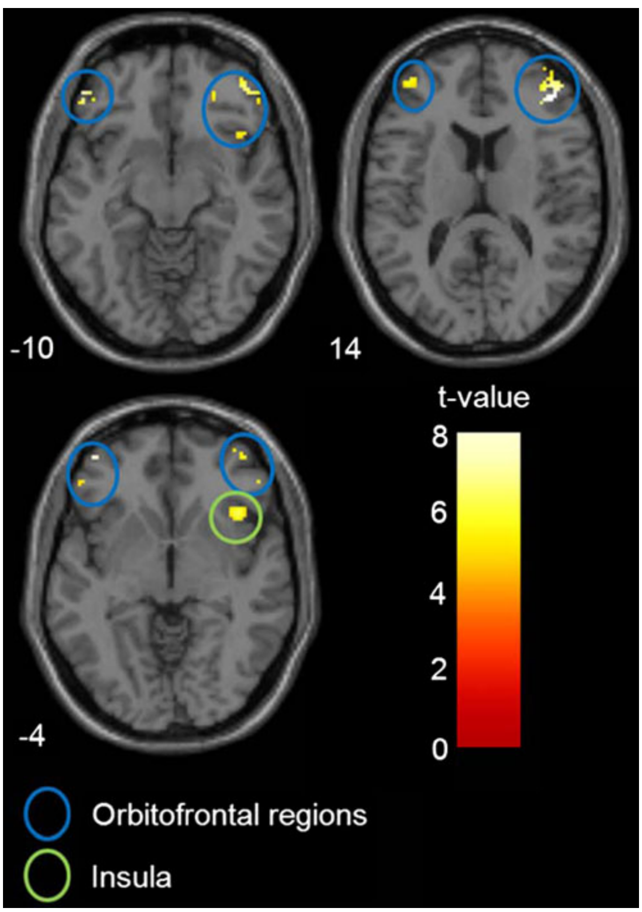

Fig. 3 Activated clusters ($k \geq 16$; p FWE corrected <0.05) for both odors (contrast—on vs. off) including all subjects. For visualization a normalized template provided by SPM 8 software (single_subj_T1.nii) was used

As partly discussed in the introduction, previous work provides only incomplete effects of handedness on the processing of olfactory information, at least with regard to odor discrimination. Here, some work suggests that odor discrimination is best at the left side in LH and vice versa (Hummel et al. 1998), while other studies suggest that handedness does not affect this task (Zatorre and Jones-Gotman 1990). Also, for odor memory tasks handedness had no simple effect on odor processing Doty et al. (1995) which is also supported by data from Gilbert et al. (1989). In addition, an Indian group also found no major influence of handedness on the ability to smell (Hebbal and Mysorekar 2003).

The current data are in line with these findings, as LH and RH participants do not differ in their central nervous activation pattern in response to two common odors, neither on the level of primary nor on the level of secondary olfactory areas. Indeed, within the current study, primary olfactory areas like

Table 1 Odor–no odor contrast across all participants (N=44); significant peaks of activation in the small volume corrected areas are presented (cluster level 16, p FWE corrected <0.05)

	MNI coordinates				
	Cluster size	t value	X	Y	Z
Orbitofrontal cortex (right)	63	7.75	42	40	14
	47	6.34	44	46	−10
	89	5.63	44	48	8
	19	5.31	24	42	−14
Orbitofrontal cortex (left)	38	7.42	−44	54	−4
	39	6.97	−50	44	−10
	20	5.52	−40	52	14
Insula (right)	105	6.09	40	22	−4

the amygdala, the piriform cortex, and the entorhinal cortex were not significantly activated in the “odor” condition. However, this is not an uncommon finding with fMRI in olfaction. There are several studies in which the amygdala (Reske et al. 2010; Wang et al. 2010) and the piriform cortex (Grabenhorst et al. 2011) have not been significantly activated by olfactory stimulation. Still our results clearly show odor-induced activation within secondary olfactory areas (insula and orbitofrontal cortex). In contrast to the pilot data of Yousem and colleagues, however, these areas were not differentially activated as a function of handedness. Moreover, even the whole brain analysis conducted additionally did not yield any differences with regard to handedness.

Thus we conclude that we find no evidence that handedness plays a major role when it comes to processing of olfactory information in relation to relatively simple olfactory tasks—as was the case with the passive olfactory stimulation in the present study. In contrast, this may change when (1) odor-related tasks become more complex and/or (2) if they involve activation of the trigeminal system (e.g., Oertel et al. 2008; Iannilli et al. 2008) which is typically the case at higher odor concentrations (Cometto-Muñiz and Cain 1992; Hummel et al. 1992). Future studies will have to tell us if, and under which circumstances, handedness is of significance in the processing of olfactory information.

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