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Human olfactory lateralization requires trigeminal activation

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ABSTRACT

Rats are able to lateralize odors. This ability involves specialized neurons in the orbitofrontal cortex which are able to process the left, right and bilateral presentation of stimuli. However, it is not clear whether this function is preserved in humans. Humans are in general not able to differentiate whether a selective olfactory stimulant has been applied to the left or right nostril; however exceptions have been reported.

Following a screening of 152 individuals with an olfactory lateralization test, we identified 19 who could lateralize odors above chance level. 15 of these "lateralizers" underwent olfactory fMRI scanning in a block design and were compared to 15 controls matched for age and sex distribution. As a result, both groups showed comparable activation of olfactory eloquent brain areas. However, subjects with lateralization ability had a significantly enhanced activation of cerebral trigeminal processing areas (somatosensory cortex, intraparietal sulcus). In contrast to controls, lateralizers furthermore exhibited no suppression in the area of the trigeminal principal sensory nucleus. An exploratory study with an olfactory change detection paradigm furthermore showed that lateralizers oriented faster towards changes in the olfactory environment. Q3 Q4

Taken together, our study suggests that the trigeminal system is activated to a higher degree by the odorous stimuli in the group of "lateralizers". We conclude that humans are not able to lateralize odors based on the olfactory input alone, but vary in the degree to which the trigeminal system is recruited.

Q5 Introduction

Like most animals, humans have the ability to track odors and follow their route (Porter et al., 2007). However, when movements are prevented, most humans are not able to localize whether an odor was presented to the left or right nostril (Kobal et al., 1989; Schneider and Schmidt, 1967). We aimed to understand what distinguishes people with and without the ability to lateralize olfactory stimuli.

As with other senses, the sense of smell is organized as a pairwise organ. Odors reach olfactory receptors in the left or right nasal cleft which are separated by the nasal septum. In contrast to other senses, at least initially olfactory activation is processed ipsilaterally to the side of stimulation (Lascano et al., 2010). The pairwise organization of the sense of smell has some consequences: First, the brain hemispheres develop specialized functions in early childhood (Chiron et al., 1997) so that activation of both hemispheres results in optimum processing of the information. While there is a left sided dominance for speech (Binder et al., 1997) it is assumed, that processing of emotional information is predominantly taking place in the right hemisphere (Schwartz et al., 1975). Accordingly, for odors, it has been reported that they are rated more pleasant when sniffed through the right nostril and identified more correct when applied through the left (Herz et al., 1999). Second, paired input helps to locate the stimulus; this ability to localize stimuli is potentially relevant for orientation. For visual, auditory and tactile stimuli, differential input to the left and right side allows to localize the source of the stimulus. For olfactory stimuli, it has been shown, that sniffing through both nostrils enhances the chance of olfactory scent tracking under natural conditions (Porter et al., 2007).

Rats are able to lateralize odors. This ability involves specialized neurons in the orbitofrontal cortex which are able to process stimuli presented to the left nostril, right nostril or both nostrils (Wilson, 1997). Sharks on the other hand seem to recruit additional peripheral information from the lateral line organ in order to locate odors (Gardiner and Atema, 2007). Because the nasal mucosa is innervated by the trigeminal nerves (Daiber et al., 2013; Schaefer et al., 2002), most odors activate not only the olfactory but, to a certain degree, also the trigeminal system. Trigeminal stimulation leads to different brain activation patterns compared to olfactory stimulation (Iannilli et al., 2013). Because trigeminal information is transported via myelinated fibers, while olfactory information is transported via unmyelinated fibers, it is no surprise that brain potentials are obtained faster for trigeminal activation (Iannilli et al., 2013).

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In order to study the human ability to lateralize odors, odorous stimuli are of interest which do not only activate the trigeminal system but also specifically produce olfactory activation. Odors are generally believed to be purely olfactory, if they cannot be detected by anosmic people. This is the case, for example, for vanillin and hydrogen sulfide, and, also to a relatively high degree, for phenyl ethyl alcohol (Doty et al., 1978; Hummel et al., 1991).

The majority of humans seem to be unable to lateralize selective olfactory stimuli. Frasnelli et al. published two studies showing that humans on average lack olfactory lateralization ability (Frasnelli et al., 2010), irrespective whether stimuli are actively sniffed or passively applied (Frasnelli et al., 2009). However, their data also indicate that some people are able to lateralize above chance (Frasnelli et al., 2010) and that an increased numbers of molecules enhances localization ability even for relatively selective olfactory stimuli, like phenyl ethyl alcohol (Frasnelli et al., 2011). Olfactory lateralization ability depends on trigeminal input (Kobal et al., 1989; Lundstrom et al., 2012) and mixed chemicals, activating both receptor types typically can be localized without problems (Frasnelli et al., 2010, 2011; Hummel et al., 2003; Kleemann et al., 2009; Schneider and Schmidt, 1967; von Békésy, 1964; Wysocki et al., 2003).

Recently we could show that training improves the lateralization ability of selective olfactory stimuli (Negoias et al., 2013). If there are some persons with lateralization ability and this can even be trained, the question arises, how the processing of olfactory information differs between people who can, and the many other people who cannot lateralize odors? We followed this question by comparing brain activation for selective olfactory stimuli in people with and without lateralization ability. As trigeminal stimuli can be lateralized, we assumed that the trigeminal system is involved in lateralization. Therefore, we focused the analysis not only on primary and secondary olfactory areas, but also on regions known to be related to trigeminal processing.

Those include primary regions involved in intranasal trigeminal perception (midbrain and pons, compare (Boyle et al., 2007; Hummel et al., 2005)) and regions typically activated after cutaneous stimulation of the trigeminal nerves (primary and secondary somatosensory cortices Eickhoff et al., 2007). Furthermore, there is a reason to assume, that the intraparietal sulcus is involved in localization of chemosensory stimuli. Frasnelli and colleagues recently compared brain activations from a localizable olfactory-trigeminal mixture with activations of a non-localizable odor (Frasnelli et al., 2012). They found the intraparietal sulcus to be involved in odor localization, while areas associated with chemosensory processing, such as insular cortex and orbitofrontal cortex showed no difference in activation. In the same line, Boyle et al. found the intraparietal sulcus to be involved in the processing of combined olfactory/trigeminal stimuli, but not in the processing of selective olfactory stimuli (Boyle et al., 2007). We therefore hypothesize, that persons with lateralization ability exhibit enhanced activation of the intraparietal sulcus.

Besides the fMRI study, an olfactory attention experiment was performed with a subsample of the participants. This study aimed to explore, whether lateralization ability enhances attention towards odors. Humans are typically rather poor in detecting changes of the olfactory environment spontaneously. The lack of egocentric spatial information is discussed as one of the reasons for this (Sela and Sobel, 2010). Consequently, one would expect that persons with lateralization ability, who have more egocentric spatial information, are more aware of the olfactory environment. We created an "olfactory change detection test" (see below), to test whether olfactory lateralization facilitates orientation towards odors.

Methods

Ethics statement

The study followed the Declaration of Helsinki on Biomedical Research Involving Human Subjects and was approved by the Ethics Committee of the TU Dresden. All participants provided written informed consent.

Participants

A total of 152 people between 18 and 40 years of age were screened for olfactory lateralization (Frasnelli et al., 2011). The test device consists of two squeezable bottles that are pressed simultaneously and deliver an airstream into both nostrils of the participant. Only one of the bottles contains an odor and therefore only one side of the nose receives olfactory input. Phenyl ethyl alcohol (20% v/v; dissolved in propylene glycol) was used for selective olfactory stimulation. The participant's task was to answer in a forced choice paradigm which side had been stimulated. The task was repeated 20 times with a random order of the side of odor presentation. Using the binominal distribution formula the likelihood to answer correctly ≥ 15 times or to answer incorrectly ≤ 5 times can be calculated to 4.2%.

Nineteen of the 152 people tested showed lateralization ability above chance (≥ 15 or ≤ 5); they were invited to participate in the fMRI study ("lateralizers"). Data is presented for those 17 lateralizers, who exhibited a score ≥ 15 (compare Fig. 1). Two of them and one of the controls were excluded because of technical problems with data acquisition or brain abnormalities. The remaining groups consisted of 15 participants in the lateralization group (9 women, 6 men, 22–36 years, mean age 25.5 ± 3.5 years) and 15 in the control group (7 women, 8 men, 24–30 years, mean age 25.9 ± 1.9 years). According to the inclusion criteria, the participants differed significantly with respect to their lateralization ability ($t[28] = 12{,}3$; $p < 0.001$). There were no significant group differences in age or sex. Although participants with lateralization ability were slightly better in olfactory thresholds, the effect was not significant ($t[28] = 1.9$; $p = 0.07$; compare Table 1).

fMRI Procedure

A 3 Tesla MR scanner (Trio; Siemens Medical, Erlangen, Germany) was used for data acquisition. Each participant was scanned in two functional sessions in a block design. In both sessions phenyl ethyl alcohol (PEA; dissolved in propylene glycol at 20% v/v; total flow per nostril 1 l/min; the off condition was solvent only) was presented in 12 on/off blocks to the right and in 12 on/off blocks to the left nostril (see Fig. 2). After each of the two sessions, participants were asked to rate the intensity of the odor on a scale from 0 (not intense at all) to 10 (extremely intense). Order of stimulus presentation in each session and order of sessions was randomized. In total, each participant received 24 on/off blocks for left and 24 for right sided stimulation. Each

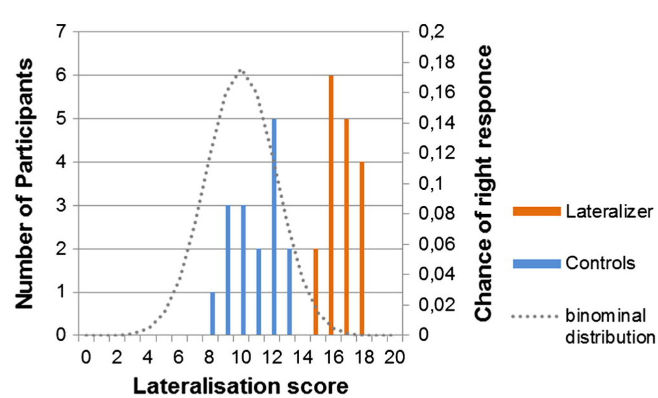

Fig. 1. Lateralisation scores of participants selected for the control and for the lateralizer group. The dashed line shows the distribution of the binominal curve. Participants within a range below 6 and above 14 are included in the control group. The area under the curve for this range is at 95.8%.

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