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Localisation of unilateral nasal stimuli across sensory systems

Johannes Frasnelli*, Valérie La Buissonnière Ariza, Olivier Collignon, Franco Lepore

CERNEC, Université de Montréal, Montréal, QC, Canada

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ABSTRACT

Odor stimuli presented to one nostril can only be localised if they additionally activate the trigeminal nerve's chemosensitive fibers. In this study we aimed to investigate characteristics in the localisation of unilateral trigeminal, olfactory and somatosensory nasal stimuli. We compared the ability of healthy young subjects to localise monorhinally presented (a) pure olfactory stimuli (phenyl ethyl alcohol), (b) mixed olfactory trigeminal stimuli (eucalyptol), and (c) somatosensory stimuli (air puffs). As expected, subjects could localise the air puffs and eucalyptol, but could not phenyl ethyl alcohol. Interestingly, we observed a significant correlation between localisation performance for eucalyptol and phenyl ethyl alcohol but not between the ability to localise somatosensory and trigeminal or olfactory stimuli. These observations show that on a behavioural level, the trigeminal chemosensory system is more intimately connected to the olfactory system than to the somatosensory system despite the fact that anatomically its information is conveyed via same nerve as the latter. Furthermore, they show that the trigeminal chemosensory system should therefore be considered a self-confined contributor to chemosensory perception.

The trigeminal system represents a third chemical sense, next to smell and taste. Its receptive structures are located in the nasal and oral cavity; it allows for perception of the burning of chilli, the cooling of mint, the sparkling of carbonated water and many more via the activation of specific chemoreceptors (such as TRPV1 [33] or TRPM8 [46]) or free nerve endings [11]. In fact, most odorous substances also activate the trigeminal system, at least in higher concentrations [12]. One interesting aspect of the intranasal trigeminal system is that it allows for localisation of monorhinally presented stimuli. Thus, we are able to correctly localise odorous stimuli which have been presented to one nostril, only if the substance also activates the trigeminal system [28,29,44]. Accordingly, we can localise mixed olfactory trigeminal stimulus, such as eucalyptol, but we cannot localise pure odors, such as the rose odor phenyl ethyl alcohol [15,29]. The term "pure odors" refers to stimuli which activate exclusively the olfactory nerve, without concomitant trigeminal stimulation. Only few pure odors are known; they include phenyl ethyl alcohol, vanillin, and decanoic acid [12].

The olfactory and the trigeminal system are closely interconnected. As mentioned above, in higher concentrations, most odors also stimulate the trigeminal system. Furthermore, simultaneous stimulation with a trigeminal stimulus decreases the intensity of an odor [9,34], probably due to a central interaction between both sensory systems [9]. In addition, subjects with a loss of olfactory function also exhibit a decreased trigeminal sensitivity [18,21,23]. Interestingly, this decreased sensitivity seems to be limited to the chemosensory portions of the trigeminal system only. When chemosensory trigeminal thresholds were compared between healthy controls and patients with olfactory dysfunction, the latter exhibited higher thresholds indicating lower sensitivity. When however somatosensory trigeminal thresholds were compared, no difference between both groups could be observed [19], although both types of information, i.e., chemosensory and somatosensory, are conveyed via the same nerve. This suggests that the close connection between olfactory system and trigeminal system is limited to the chemosensory portions of the latter. In other words, the two sensory portions of the trigeminal nerve, i.e., the chemosensory and the somatosensory system seem to be relatively independent from each other.

Because of these close connections between trigeminal and olfactory functions and the relative independence between trigeminal and somatosensory functions, we designed a study to further understand the relations between these sensory systems in our ability to localise odors. We thus monorhinally presented our subjects with (1) a pure odor, (2) a mixed olfactory trigeminal stimulus, and (3) a somatosensory stimulus.

We hypothesized that subjects could localise both stimuli which activate the trigeminal nerve, i.e., the mixed olfactory trigeminal stimulus and the somatosensory stimulus, but not the pure odor. As a consequence of the relative independence of the dif-

* Corresponding author at: Université de Montréal, Département de Psychologie, Salle F-475, Pavillon Marie-Victorin, 90, ave. Vincent-d'Indy, Montréal, Québec, H2V 2S9, Canada. Tel.: +1 514 343 6111x10705; fax: +1 514 343 5787.
E-mail address: frasnelli@yahoo.com (J. Frasnelli).

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ferent trigeminal fiber subtypes, we hypothesized the results for the somatosensory and the mixed olfactory trigeminal stimulus not to be correlated. In contrast, we expected the results for the pure odorant and the mixed olfactory trigeminal stimulus to be correlated, as an expression of the intimate connection between both chemosensory systems.

The study was conducted in agreement with the Declaration of Helsinki. Subjects gave informed written consent prior to testing. The protocol was approved by the Ethics Board of the University of Montreal.

Subjects: We included 32 subjects (14 women) aged between 18 and 35 years (mean age 23 ± 3 (SD) years). No participant suffered of any medical conditions at the time of the testing and did not report any olfactory problems.

Stimuli: We used pure eucalyptol (eucalyptus odor; Galenova, St.-Hyacinthe, QC) and phenyl ethyl alcohol (rose odor; SAFC, St. Louis, MO) as chemosensory stimuli, and air puffs as somatosensory stimuli. Eucalyptol has a distinctive smell; it can however clearly be perceived by anosmic subjects [23,30], probably via the trigeminal receptor TRPM8 [2]. It is therefore considered to be a mixed olfactory trigeminal stimulus. Phenyl ethyl alcohol on the other hand cannot be perceived by anosmic subjects [12] and is therefore considered a pure odorant which activates the olfactory nerve exclusively. The air puffs, on the other hand, activate only somatosensory trigeminal fibers.

Stimulus presentation: We adapted an fMRI compatible tactile stimulator (Institute for Biomagnetism and Biosignalanalysis, University of Münster, Germany) in order to present stimuli in an automated fashion. This portable multi-channel stimulator is designed for generation and delivery of constant air puffs for somatosensory stimulation during MEG and fMRI acquisition [14]. The stimulator provides air pressure pulses of well defined duration. Instead of connecting the outlets to balloon diaphragms, as it is done for tactile stimulation, we connected them to odor chambers via polyurethane tubing with 8 mm outer diameter and an inner diameter of 4.8 mm (Fre-Thane 85A, Freelin-Wade, McMinnville, OR). The odor chambers were glass bottles with a volume of 50 mL and were filled with 4 mL of odorant. The outlet of the odor chambers was then connected to the subjects' nose by means of the same polyurethane tubing of approximately 50 cm length. By keeping all tubings separated we could avoid cross contamination of odors. During odor presentation, air with a flow of 2 L/min was switched into the respective channel. All stimuli lasted 750 ms. Therefore, subjects were stimulated with 25 mL of air per stimulated nostril.

Procedure: Subjects were blindfolded during the whole experiment. Stimuli were delivered to one nostril (monorhinal stimulation). When pure odor (phenyl ethyl alcohol) and mixed olfactory trigeminal (eucalyptol) stimuli were presented to one nostril, an odor free air puff, equivalent in terms of pressure and duration, was simultaneously delivered to the other nostril, so that the subjects could not use somatosensory cues to localise the stimuli. An alerting high pitch (150 ms) was delivered that announced the arrival of the next stimulus during a time interval of 2–4 s after the alerting sound. In order to standardise the exploration of the stimuli, subjects were asked to breathe when hearing the alerting acoustic signal, hold the breath during stimulus presentation, and breathe again after they had given their answer. After stimulus presentation, subjects' task was to press one of two buttons as fast as they could in order to indicate if they had perceived the stimulus in the left or the right nostril. The next stimulus cycle started after a resting period of 8000 ms.

Subjects carried out 2 blocs of 48 pseudo-randomized stimuli (8 times the 6 different stimuli) and thus received a total of 96 stimuli for the whole experiment (32 each for air puffs, eucalyptol and phenyl ethyl alcohol).

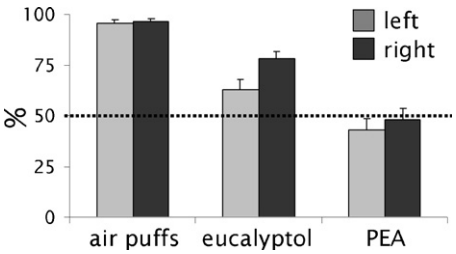

Fig. 1. Mean results (in %) when localising presented air puffs, eucalyptol stimuli and phenyl ethyl alcohol (PEA) stimuli to the left and the right nostril. The dotted line represents chance performance.

Stimulus delivery and responses recording were controlled by the "Presentation" software (Neurobs) running on a HP PC (AMD Phenom X3 processor) with Windows XP. Performances of the subjects were evaluated in terms of hit rates (proportion of correct responses).

Statistical analysis: The statistical analysis was performed by means of SPSS 16.0 (SPSS Inc., Chicago, IL). First, we compared the performance against chance level using binomial statistics. Then, we calculated repeated measures (rm) ANOVA on the dependent variable "hit rate" with "stimulus" (phenyl ethyl alcohol, eucalyptol, air puff), "nostril" (left, right) as within subject factors. We also included "sex" (women, men) as between subject factor. We computed post hoc *t*-tests when the ANOVA indicated significant main effects. Furthermore, we calculated Spearman's ranked correlation coefficient between scores obtained for the different stimuli as well as scores for the left and right nostril. In order to estimate task accuracy we computed the sensitivity index d' and response bias criterion c, according to the signal detection theory [40]. Criterion c can range from −1 to +1. A c of 0 denotes no tendency; negative values signify a tendency to the right, positive values signify a tendency to the left. Significance level was set at 0.05.

Air puffs and eucalyptol were localised above chance (binomial; air puffs: $p < 0.001$; eucalyptol: $p = 0.03$) while phenyl ethyl alcohol was localised at chance.

In the rmANOVA we observed a significant effect of "stimulus" ($F[2,58] = 110$; $p < 0.001$), indicating that air puffs were better localised than eucalyptol (air puffs: 91.3 [SEM: 1.9]%; eucalyptol: 68.1 [3.2]%; post hoc: $p < 0.001$) and that eucalyptol was better localised than phenyl ethyl alcohol stimuli (41.8 [3.2]%; post hoc: $p = 0.001$).

The factor "side" failed to reach significance ($F[1,30] = 3.1$; $p = 0.088$). However, side differences have been reported in earlier studies; we thus compared the results for both nostrils for any given stimulus. In fact, when using eucalyptol, subjects performed significantly better on the right nostril (75.4 [3.6]%) than on the left nostril (60.9 [4.8]%, $p = 0.017$; uncorrected). Although we also observed higher scores on the right nostril for the other stimuli, these differences were not significant (Fig. 1).

We did not observe sex differences and no significant interactions between factors.

Since the results for air puffs were not normally distributed (Kolmogorov–Sminorff: $p = 0.047$), we next computed Spearman's ranked coefficient in order to investigated whether the scores obtained for the different stimuli were correlated. Here, we observed the results for eucalyptol and phenyl ethyl alcohol to be correlated (rho[32] = 0.458; $p = 0.008$). In contrast, scores for air puffs were not correlated neither to eucalyptol nor phenyl ethyl alcohol scores (Fig. 2).

When looking at the single nostrils, we observed a significant correlation for the results on the left and the right nostril, when air puffs were used as stimuli (rho[32] = 0.363; $p = 0.041$), indicating that subjects who performed well when localising air puffs on the

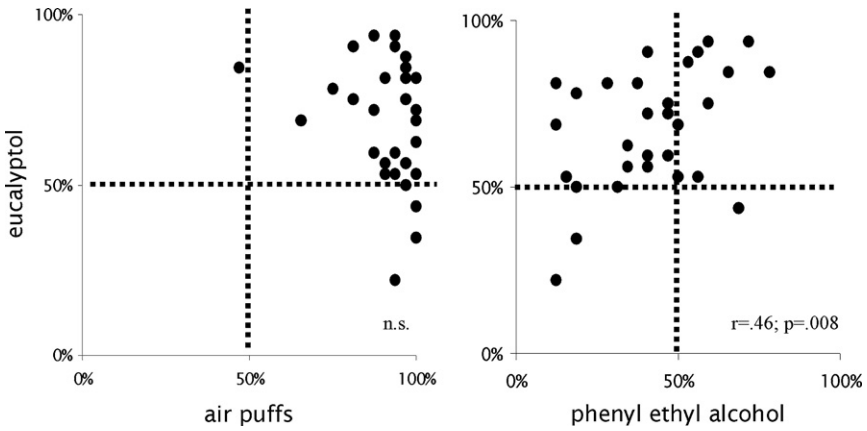

Fig. 2. Individual scores when localising monorhinally presented stimuli. On the *y*-axis, the scores for eucalyptol are represented. On the *x*-axis scores for air puffs (left diagram) and phenyl ethyl alcohol (right diagram) are depicted. Dotted lines represent chance performance.

right nostril, were good in doing so with left sided stimulation, too. No such correlation between left and right nostril was observed for eucalyptol or phenyl ethyl alcohol. In contrast, we observed a significant correlation between results for eucalyptol and phenyl ethyl alcohol stimulation in the left nostril ($r[32] = 0.491$; $p = 0.004$) and in the right nostril (rho[32] = 0.509; $p = 0.003$). This indicates that subjects were better in localising eucalyptol in a given nostril also performed better for phenyl ethyl alcohol in the same nostril. We did not observe such a correlation between air puffs and both chemosensory stimulations.

On average, we observed a rightward tendency in all conditions, which was smallest for the air puffs (−0.034), larger for phenyl ethyl alcohol (−0.13), and largest for eucalyptol (−0.24). We observed the rightward tendency to be significantly correlated for eucalyptol and phenyl ethyl alcohol ($r[32] = 0.57$; $p = 0.001$). There was no such correlation for air puffs.

For the present study, we were able to design a fully automated delivery system to carry out an olfactory localisation task. Compared to the usually used manual devices [23,45], an automated delivery system has the advantage to not be influenced by subject-tester interactions and to ensure perfect time-control.

By using this device we compared for the, to the best of our knowledge, first time, subjects' ability to localise monorhinally presented pure olfactory stimuli, trigeminal chemosensory stimuli, and trigeminal somatosensory stimuli in the same study. We observe participants to be able to localise eucalyptol stimuli and air puffs, but not phenyl ethyl alcohol stimuli. This is in line with previous reports on the ability of humans to localise chemosensory stimuli. In contrast to, e.g., rats [36], we are able to localise odorous stimuli only if they additionally stimulate the trigeminal nerve [15,28,29,44,49]. In the present study for the first time we analyzed correlations between performances in different sensory systems while localising monorhinal stimuli; interestingly, we observed the results for both chemosensory stimuli (phenyl ethyl alcohol and eucalyptol), but not for eucalyptol and air puffs to be significantly correlated. This correlation between scores obtained with eucalyptol and phenyl ethyl alcohol is notable if one considers the fact that, on average, subjects' performance when localising the pure olfactory stimulus phenyl ethyl alcohol was slightly below chance, in line with earlier reports [15,20,39]. In order to explore this correlation closer, we looked at subsets of subjects. We observed the 10 subjects performing above chance with phenyl ethyl alcohol as stimulus, with an average score of 62%, to also have a superior average performance of 80% with eucalyptol as the stimulus. Thus one may speculate that subjects who are very sensitive when localising eucalyptol may in fact also be able to localise phenyl ethyl alcohol. Those 10 subjects with the lowest scores for phenyl ethyl alcohol (average score: 21%) on the other hand could localise eucalyptol in only 58% of the trials. Their score for phenyl ethyl alcohol was so low that one could speculate that they are actually able to localise it, but to the wrong side. Keeping this in mind, it would be interesting to know if any of these subject groups could be trained to localise phenyl ethyl alcohol, e.g., in a feedback paradigm [45].

We know that the olfactory and the trigeminal system suppress and enhance each other mutually [9,34]. One could speculate that, in analogy, the olfactory input may reduce also the somatosensory sensation. In this scenario, on the stimulated side, the olfactory stimulation would lead to a reduced somatosensory sensation as compared to the other nostril, where only an air puff was delivered. If no additional chemosensory trigeminal input occurs simultaneously, the subject may localise the sensation on the side where no olfactory stimulation had taken place, and thus to the wrong side. There is further evidence that olfactory input may interfere with odor localisation. In a study on the trigeminal properties of the putative human pheromone androstadienone (AND), Boyle and colleagues observed that subjects who were anosmic to AND were better in localising it in a paradigm similar to the one we used. Subjects who could perceive the olfactory components of AND however performed poorer localising AND [5]. Further research is needed to put these different observations into one theoretical framework.

We observed a rightward response tendency, in line with research from other sensory areas such as audition [13,31,32]. In the visual domain, when subjects bisect horizontal lines, they generally lateralize the vertical center to the left. This is thought to represent a rightward shift in the perceived location of this central point [3,6,7], reflecting a structural specialization of the right cerebral hemisphere for spatial attention [35], which induces a tendency to localise uncertain spatial percept to the weaker right hemifield. However we observed the tendency to the right to be only minimal for the somatosensory stimulus and most prominent for the mixed olfactory trigeminal chemosensory stimulus. Again, we observed a significant correlation between the response bias (rightward tendency) for both chemosensory stimuli, but not for the somatosensory stimuli. A right-sided advantage/tendency in the olfactory system has been found with regards to olfactory discrimination [37,47], olfactory thresholds [8], and odor memory [27]. In addition, there is a right hemispheric predominance in olfactory processing [17,38,48]. In addition to these olfactory tasks, there is also a rightward tendency in tasks involving the trigeminal chemosensory system [15]. We know that even pure trigeminal chemosensory stimuli in addition to somatosensory brain areas activate brain regions which are usually involved in the processing of olfactory stimuli, including orbitofrontal, piriform and insular cortex [1,4,22], mainly in the right hemisphere [4,24]. An intimate

connection between olfactory and chemosensory has also been shown functionally. If the sense of smell is impaired trigeminal chemosensory sensitivity is also reduced. This has been shown by means of psychophysical methods [18,23], electrophysiological measures [18,21], and brain imaging techniques [26]. From our results one could therefore conclude that side effects are another common feature of the trigeminal chemosensory system and the olfactory system.

It is unquestionable that a successful localisation of eucalyptol is based on the activation of intranasal trigeminal fibers. Here we compared subjects' ability to localise trigeminally mediated chemosensory and somatosensory stimuli. Interestingly we did not observe a correlation in subjects' ability to localise air puffs and chemosensory stimuli, although in both cases the necessary information is conveyed via the same cranial nerve. However, there are a number of reports on dissociations between the chemosensory and the somatosensory portions of the trigeminal nerve. We know, for example, that different regions of the nasal mucosa respond differently to chemosensory and somatosensory trigeminal stimulation. After stimulation with carbon dioxide (chemosensory stimulation) larger cerebral electrophysiological responses and greater intensity ratings were obtained after stimulation of the anterior portion of the nasal cavity, when compared to the posterior one. For air puffs (somatosensory stimulation), this was the other way round [16]. A similar dissociation between somatosensory and chemosensory sensitivity has been observed in patients with anosmia, who are known to also exhibit reduced chemosensory trigeminal sensitivity [21,23,42,43]. Thus, as expected, patients with anosmia exhibited higher chemosensory thresholds when compared to controls. However, patients and controls had similar thresholds to (somatosensory) electrical cutaneous stimulation [19]. Finally, differences between chemosensory and somatosensory trigeminal perception have been described with regards to brain activation patterns. Intranasal trigeminal chemosensory stimulation leads to activations of brain regions which are usually activated after olfactory and/or gustatory stimulation, such as the orbitofrontal cortex, piriform cortex and insula [1,4]. After somatosensory stimulation activation of these brain areas is usually not observed [10]. In fact, a direct comparison between chemical (carbon dioxide) and mechanical (air puffs) trigeminal stimulation revealed that the former led to a significantly higher activation in the left insula and the right frontal lobe [25].

In summary, we show that the ability to correctly localise a monorhinally presented trigeminal chemosensory stimulus is not related to the ability to localise a somatosensory stimulus but rather to the localisation of an olfactory stimulus. Both the localisation of trigeminal chemosensory stimuli and olfactory stimuli share a tendency for a right-sided bias. From the literature we know that the chemosensory trigeminal and the olfactory system share neuroanatomical [1,4] and functional [21,23,41,43] characteristics. On the other hand, the somatosensory and the chemosensory portions of the trigeminal nerve have been shown to exhibit different characteristics on neuroanatomical [25] and functional [19] levels. Together with earlier reports our results therefore further support the notion of an intimate connection between the chemosensory trigeminal and olfactory systems.

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