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## Review

## The neuronal correlates of intranasal trigeminal function—an ALE meta-analysis of human functional brain imaging data

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## ARTICLE INFO

## Article history:

Accepted 4 November 2009

Available online 11 November 2009

## Keywords:

Activation likelihood estimation

Olfaction

Nose

Somatosensory

fMRI

PET

## ABSTRACT

Almost every odor we encounter in daily life has the capacity to produce a trigeminal sensation. Surprisingly, few functional imaging studies exploring human neuronal correlates of intranasal trigeminal function exist, and results are to some degree inconsistent. We utilized activation likelihood estimation (ALE), a quantitative voxel-based meta-analysis tool, to analyze functional imaging data (fMRI/PET) following intranasal trigeminal stimulation with carbon dioxide (CO<sub>2</sub>), a stimulus known to exclusively activate the trigeminal system. Meta-analysis tools are able to identify activations common across studies, thereby enabling activation mapping with higher certainty. Activation foci of nine studies utilizing trigeminal stimulation were included in the meta-analysis. We found significant ALE scores, thus indicating consistent activation across studies, in the brainstem, ventrolateral posterior thalamic nucleus, anterior cingulate cortex, insula, precentral gyrus, as well as in primary and secondary somatosensory cortices—a network known for the processing of intranasal nociceptive stimuli. Significant ALE values were also observed in the piriform cortex, insula, and the orbitofrontal cortex, areas known to process chemosensory stimuli, and in association cortices. Additionally, the trigeminal ALE statistics were directly compared with ALE statistics originating from olfactory stimulation, demonstrating considerable overlap in activation. In conclusion, the results of this meta-analysis map the human neuronal correlates of intranasal trigeminal stimulation with high statistical certainty and demonstrate that the cortical areas recruited during the processing of intranasal CO<sub>2</sub> stimuli include those outside traditional trigeminal areas. Moreover, through illustrations of the considerable overlap between brain areas that process trigeminal and olfactory information; these results demonstrate the interconnectivity of flavor processing.

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## 1. Introduction

Everyday chemosensory processing is based partly on the interaction between two systems, the olfactory and the trigeminal system. Whereas the olfactory system mediates the quality percept of an odor, the trigeminal system conveys sensations such as a burning, pungency, or stinging, as well as touch, pressure, and temperature. Although the processing of olfactory stimuli has received much attention, the neurological substrate of intranasal trigeminal function remains poorly understood. Further investigations of the intranasal trigeminal system are of great importance to an understanding of its role as a sentinel against potentially toxic substances and as the mediator of more animated percepts of odors and flavors.

Our current understanding of mechanisms underlying trigeminal stimulus processing is derived mostly from animal models (for review see Langley et al., 2008; Mogil, 2009). In both animals and humans, the nasal mucosa is innervated by the ophthalmic and maxillary branches of the trigeminal nerve, which transfers information about a painful stimulus to trigeminal nuclei in the spinal cord (Anton et al., 1991). From there, information is relayed via the lateral and the medial pain systems, two parallel organized systems with distinct projections (de Leeuw et al., 2005). The lateral pain system transmits information to lateral thalamic structures, which project to the primary (S I) and secondary (S II) somatosensory cortices. The medial pain system transfers information to medial thalamic nuclei and from there to prefrontal cortex, insula, cingulate gyrus, brain stem, and to the limbic system (Ingvar and Hsieh, 1999; Treede et al., 1999; Wiech et al., 2001). Significant genetic, neurochemical, and neuroanatomical differences distinguish non-human and human processing and experience of pain-related stimuli, as demonstrated by recent findings (Craig, 2009). Among other implications, these conclusions suggest that although animal models may provide an approximation of basic human trigeminal processing, there is no substitute for human subjects in the quest to

reach a full understanding of how the human brain processes trigeminal stimuli.

Investigations of the human trigeminal system frequently rely on psychophysical or electrophysiological methods (Hari et al., 1997; Hummel and Kobal, 1999; Hummel and Livermore, 2002; Huttunen et al., 1986; Kobal and Hummel, 1988; Rombaux et al., 2006), which yield results that allow only indirect inferences of underlying cerebral processes due to methodological limitations. Psychophysical and electrophysiological tools lack direct links to functional processing and provide low spatial specificity. In contrast, non-invasive methods of functional brain imaging allow us to understand trigeminal processing with higher spatial resolution. In conjunction with these methods, the use of pure trigeminal stimuli, typically carbon dioxide (CO<sub>2</sub>), an odorless gas that stimulates the trigeminal system almost exclusively, enables isolation of an intranasal trigeminal sensation from an accompanying odor sensation (Fröhlich, 1851; Shusterman and Balmes, 1997; Stevens et al., 1982; Thürauf et al., 1991). Similarly, studies investigating olfactory processing often opt to use pure odorants that do not stimulate the trigeminal system, such as phenyl ethyl alcohol (PEA) or hydrogen sulfide (H<sub>2</sub>S) (Doty et al., 1978; Kobal et al., 1989).

Several comparisons of brain activation originating from stimulation with pure trigeminal stimuli to activation originating from stimulation with pure odorants have demonstrated considerable overlap in the structures mediating functional processing in each system (Boyle et al., 2007; Hummel et al., 2005, 2009a,b; Iannilli et al., 2008; Schoepf et al., 2009). Whereas pure trigeminal stimuli typically activate the brain stem, thalamus, caudate nucleus, anterior and dorsolateral orbitofrontal cortex, medial frontal gyrus, frontal operculum, superior temporal gyrus, cingulate, and the postcentral gyrus, stimulation with pure odors commonly induces activation in the medial orbitofrontal cortex, amygdala, parahippocampal gyrus, and cerebellum, exclusively. Functional overlaps between the trigeminal and olfactory networks were observed in the

piriform cortex, the medial orbitofrontal cortex, peri-insular regions, as well as secondary somatosensory cortex (Boyle et al., 2007; Hummel et al., 2009b). Additional evidence for a close connection between the two chemosensory systems arises from comparisons of normosmic with anosmic subjects: trigeminally-mediated information is processed differently in the presence or absence of an intact sense of smell (Frasnelli and Hummel, 2007; Frasnelli et al., 2007; Hummel et al., 1996; Iannilli et al., 2007). Comparisons of trigeminal and olfactory imaging data have further revealed that trigeminal brain activations are often more pronounced than their olfactory counterparts (Bensafi et al., 2008; Boyle et al., 2007; Hummel et al., 2005), supporting evidence that the two systems differ with respect to intensity coding. Intensity coding in the olfactory system proceeds via a complex integrative system involving the cerebellum, entorhinal cortex, visual areas, and frontal regions, whereas the network involved in coding trigeminal stimulus intensity appears to be less complex and primarily recruits various subregions of the cingulate cortex (Bensafi et al., 2008).

Such functional imaging studies offer promising leads in the pursuit to understand intranasal trigeminal perception, however, only a limited number of these studies exist and their results are somewhat inconsistent. Due to the complex sensory and cognitive mechanisms involved in trigeminal processing, these studies often yield intricate and widespread neurological patterns rendering definitive conclusions difficult. And, though reviews of the functional imaging literature are well-suited to find activations common across studies based on a given variable of interest, much of the information about these activation patterns contained in the voxel-based data is lost in the transition from three- to two-dimensional space. A functional location meta-analysis can accomplish the three-dimensional comparison that a literature review cannot. This tool allows for a formal statistical integration of unbiased voxel-based data from multiple studies not only to determine common activations, but to provide a formal estimate of activation likelihood. Meta-analyses enable searches of emergent patterns undetectable in individual reports by providing objective methods for the post-hoc merging of data from several datasets. By utilizing a new meta-analysis tool, the activation likelihood estimation (ALE), we analyzed the datasets of functional imaging studies investigating stimulation of the nasal mucosa with CO<sub>2</sub>.

The aim of this meta-analysis was to map the human neuronal correlates of intranasal trigeminal stimulation with high statistical certainty. Cortical areas recruited during the processing of intranasal CO<sub>2</sub> stimuli were expected to include both, those known for the processing of intranasal nociceptive stimuli and those known for the processing of common olfactory stimuli. A subsequent meta-analysis intended to further compare patterns of brain activation following trigeminal with that following olfactory stimulation.

## 2. Results

### 2.1. Results of literature search

Our literature search criteria identified a total of 15 original functional imaging studies. However, only nine of those

fulfilled all stipulated inclusion criteria, as outlined in the method section, and were included in the meta-analyses. These nine studies, eight fMRI studies and one PET study (Table 1), rendered a total ten contrasts (nine fMRI contrasts, one PET contrast) and 207 activation foci.

An overview of the studies included in the olfactory ALE can be found in Table 2. Care was taken to balance the number of included contrasts and imaging modality as both can influence ALE analyses. Eight studies investigating mere olfactory stimulation-derived activation with a total of ten contrasts (nine fMRI contrasts, one PET contrast) and 119 foci were included in the olfactory ALE.

### 2.2. Significant ALE values for trigeminal stimulation

The ALE analysis revealed 29 significant clusters for intranasal trigeminal stimulation with CO<sub>2</sub>, the largest of which contained six local maxima (Fig. 1, Table 3).

We found significant ALE scores in a network known for the processing of intranasal nociceptive stimuli—the brainstem (mesencephalic trigeminal nucleus), ventrolateral posterior thalamic nucleus, thalamic tract, anterior cingulate cortex, insula and adjoining frontal operculum, superior parietal lobule, precentral gyrus, as well as primary (S I) and secondary (S II) somatosensory cortices. Significant ALE values were also observed in the piriform cortex (Fig. 4a), insula and adjoining orbitofrontal cortex (OFC) in area 13l, and the cerebellum, all areas known to process chemosensory stimuli. In addition, high ALE values were observed in association cortices, such as inferior, middle, and superior frontal gyri, as well as superior temporal gyrus and supramarginal gyrus.

### 2.3. Comparison of trigeminal and olfactory ALE maps

We initially explored which areas are more likely to be activated by trigeminal stimulation than by olfactory stimulation by contrasting trigeminal to olfactory activations. Significant ALE values, related to higher likelihood for trigeminal stimulation were found in the brainstem, insula, frontal operculum, superior parietal lobule, precentral gyrus, and primary (S I) and secondary (S II) somatosensory cortices. In addition, high significant ALE values were found in parts of the orbitofrontal cortex (posterior parts in area 13l) and the cerebellum, areas known to process chemosensory stimuli, and in association cortices (inferior, middle, and superior frontal gyri, superior temporal gyrus, supramarginal gyrus) (Figs. 2 and 4, Table 4).

For the reversed contrast, indicating which areas are more likely to be activated by olfactory stimuli than by trigeminal stimuli significant ALE scores were located in the posterior (temporal) portion of the piriform cortex, amygdala, thalamus, and anterior areas of the orbitofrontal cortex (area 13m), all of which are often reported in olfactory imaging studies. Additionally, high ALE scores were demonstrated in the frontal operculum, anterior cingulate gyrus, and parietal occipital transition area (Figs. 2 and 4, Table 4).

Overlap in brain activation maps are most commonly explored using conjunction analyses (Nichols et al., 2005). Because conjunction analysis is not yet implemented in the ALE software, we tentatively explored significant areas

**Table 1 – Studies included in the meta-analysis about intranasal trigeminal stimulation.**

Reference	Imaging modality	n	Age of the subjects (mean/range)	Side of stimulation	Concentration of CO <sub>2</sub> stimuli	Contrast (tasks)	Correction for whole brain volume	Number of contrasts	Number of foci
<i>(a) Published work</i>									
Boyle et al., 2007	fMRI (1.5 T)	15	35.3 years/23–59 years	L/R	60%	CO <sub>2</sub> L>BL/ CO <sub>2</sub> R>BL	<i>p</i> <0.001 uncorrected	2	22
Iannilli et al., 2007	fMRI (1.5 T)	12	61 years	R	60%	CO <sub>2</sub> >BL	<i>p</i> <0.001 uncorrected	1	20
Bensafi et al., 2008	fMRI (1.5 T)	8	27.5 years	R	37%/49%	CO <sub>2</sub> >BL	<i>p</i> <0.005 uncorrected	1	10
Iannilli et al., 2008	fMRI (1.5 T)	18	31 years	R	60%	CO <sub>2</sub> >BL	<i>p</i> <0.002 uncorrected	1	21
Hummel et al., 2009a,b	<sup>15</sup> O-H <sub>2</sub> O-PET	12	36 years/30–58 years	L	60%	CO <sub>2</sub> >BL	<i>p</i> <0.001 uncorrected/ <i>p</i> <0.05 SVC	1	10
Schoepf et al., 2009	fMRI (3 T)	22	29.0 years	L+R	50–60%	CO <sub>2</sub> >BL	<i>p</i> <0.005 FDR corrected	1	42
<i>(b) Unpublished work</i>									
CO <sub>2</sub> slightly painful	fMRI (1.5 T)	26	28.4 years/22–38 years	L	25–55%	CO <sub>2</sub> >BL	<i>p</i> <0.05 FWE corrected	1	30
CO <sub>2</sub> severely painful	fMRI (1.5 T)	30	27.6 years/21–38 years	L	45–60%	CO <sub>2</sub> >BL	<i>p</i> <0.05 FWE corrected	1	26
CO <sub>2</sub> 3 concentrations	fMRI (1.5 T)	27	28.9 years/22–42 years	L	40–70%	CO <sub>2</sub> >BL	<i>p</i> <0.05 FWE corrected	1	26
								10	207

commonly activated by olfactory and trigeminal stimulation by superimposing the olfactory and trigeminal ALE map on our anatomical template. The resulting images demonstrated clear overlaps of significant ALE values in piriform cortex, insula, and middle frontal gyrus, as well as a minor overlap located in orbitofrontal cortex areas 13l and 13m (Figs. 3 and 4).

### 3. Discussion

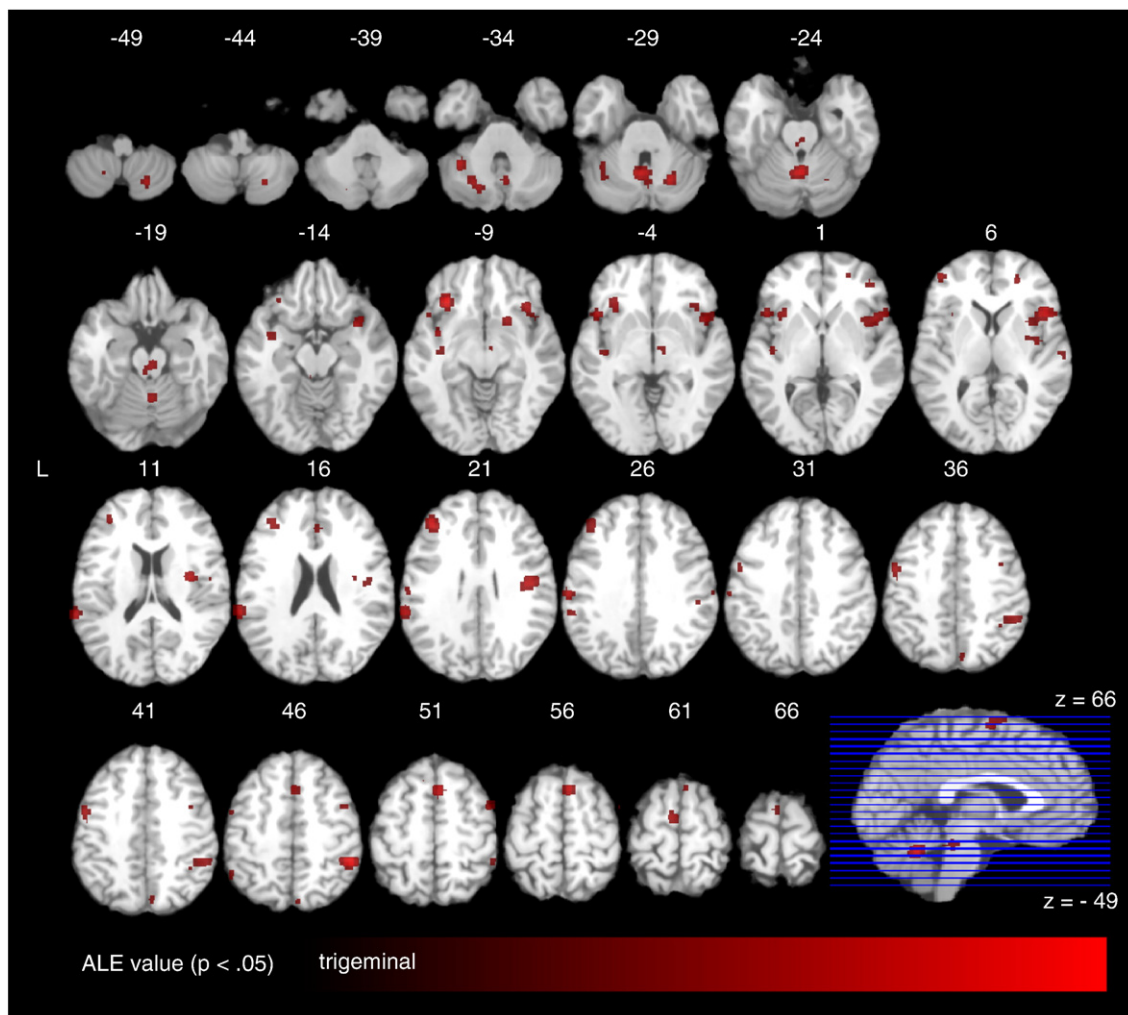
The use of a meta-analytical approach to any comparison of functional imaging datasets enables the mapping of cerebral activity with high statistical certainty because the ALE method excludes activations infrequently reported across studies. Using ALE meta-analysis, we provide a detailed *in vivo* mapping of human brain areas responsive to intranasal trigeminal stimulation.

#### 3.1. Activation of the pain network by trigeminal stimuli

As hypothesized, results of the meta-analysis confirm that intranasal trigeminal stimulation activates areas of the human brain commonly associated with nociceptive stimuli. Significant ALE values were observed in a network encompassing the brainstem, the thalamus, the anterior cingulate cortex, the insula and adjoining operculum, the superior parietal lobule, the precentral gyrus, and the primary (S I) and secondary (S II) somatosensory cortices, areas known for the processing of intranasal nociceptive stimuli (Bensafi et al., 2008; Boyle et al., 2007; Hari et al., 1997; Hummel et al., 2005, 2009b; Huttunen et al., 1986; Iannilli et al., 2007, 2008). Furthermore, published findings indicate that these areas process other painful stimuli applied to either the face (de Leeuw et al., 2005;

de Leeuw et al., 2006; Ettlin et al., 2009; Iannilli et al., 2008) or hand (Bornhovd et al., 2002; Kwan et al., 2000; Peyron et al., 2000). In conjunction with these findings, our data suggest that the processing of intranasal CO<sub>2</sub> stimulation does not utilize a unique network but rather accesses the general pain processing network, also known as the pain matrix. The functional significance of this network has been extensively reviewed elsewhere (for thoughtful reviews see May, 2007; Seifert and Maihofner, 2009; Tracey, 2008). The insula, however, appears to be activated by intranasal trigeminal stimulation uniquely, when compared to painful cutaneous electrical and irritating cutaneous mechanical stimulation of the right forehead (Iannilli et al., 2008), thereby possibly occupying a central position in the network that processes intranasal trigeminal stimuli.

The notion that peri-insular regions play an important role in the processing of intranasal trigeminal stimuli is supported by the finding that the largest cluster containing significant ALE scores was observed not in the somatosensory areas (SI or SII), as expected, but in peri-insular areas: the frontal operculum and the insular cortex. Pain perception is commonly divided into the sensory-discriminative and affective-motivational components (Treede et al., 1999). The sensory-discriminative component describes the localization of the painful stimulus as well as evaluation of intensity and quality. The emotional, arousal, and behavioral responses to a painful experience are described as the affective-motivational component of pain perception. There is evidence that the activation of the insula, particularly activation of the anterior insula, is related to the affective-motivational factor of pain perception (Craig, 2009; de Leeuw et al., 2005; Treede et al., 1999). Further support of the involvement of the insular cortex in processing pain-related emotions is provided by a set of



**Fig. 1** – Localization of significant FDR corrected ( $p < 0.05$ ) ALE values due to intranasal trigeminal stimulation with  $\text{CO}_2$  (contrast “ $\text{CO}_2$  versus Baseline”). The ALE values are projected onto a standard template (colin1.1.nii) and are shown in Talairach space ( $z = -49$  to  $66$ ,  $L = \text{left}$ ).

studies investigating empathy or compassion for pain (Danziger et al., 2009; Immordino-Yang et al., 2009; Ochsner et al., 2008; Singer, 2007). We propose the hypothesis that the insular processes emotions linked to the perception of a chemosensory stimulus and consequently plays a major role in the overall processing of intranasal trigeminal stimuli. In light of this, the role of the insula in the processing of intranasal trigeminal stimuli may be of greater importance than the roles of the somatosensory cortices and the traditional pain network.

The existing literature contains evidence that insular activation is significantly reduced when subjects are distracted during pain perception (Brooks et al., 2002), and the heterogeneous insular cortex has been suggested to act as an integration area for chemosensory stimuli (Treede et al., 1999). In this context, the large cluster of significant ALE maxima in insular cortex may result from either an attentional shift directed towards the painful, and therefore salient, stimulus or from the proposed role of the insular cortex in sensory integration. Nevertheless, these findings confirm the

central role of the insular cortex in trigeminal stimulus processing and in our understanding of the cerebral processes resulting from intranasal trigeminal stimulation.

Large clusters of significant ALE values were also observed in middle frontal and superior temporal gyri, two areas typically reported as association cortex for the processing of intranasal chemosensory stimuli (Cerf-Ducastel and Murphy, 2006; Kettenmann et al., 1997; Plailly et al., 2007; Porter et al., 2005). These authors suggested that chemosensory perception, localization, discrimination, and recognition memory lead to an activation in these areas. However, the function of these areas with respect to either trigeminal or chemosensory processing is not well explored.

Smaller clusters of significant ALE scores were localized to multiple sites within the cerebellum. Sobel and colleagues (1998b, 2000) have hypothesized that the cerebellum modulates sniff volume in relation to odor concentration, a theory supported by several reports of cerebellar activation resulting not only from odorant stimulation and sniffing of non-odorized air (Albrecht et al., 2009; Savic et al., 2002; Sobel et

**Table 2 – Olfactory functional imaging studies included in the comparison of significant ALE values between trigeminal and olfactory stimulation.**

Reference	Imaging modality	n	Age of the subjects (mean/range)	Number of contrasts	Number of foci
Gottfried and Dolan 2003	fMRI (2 T)	17	22–34 years	1	11
Gottfried et al., 2002	fMRI (2 T)	17	23 years/18–31 years	2	8
Osterbauer et al., 2005	fMRI (3 T)	10	27 years/22–35 years	1	6
Savic et al., 2000	<sup>15</sup> O-H <sub>2</sub> O-PET	18	22–27 years	1	5
Sobel et al., 2000	fMRI (1.5 T)	8	25 years/20–39 years	1	32
Wang et al., 2005	fMRI (3 T)	11	24 years/21–26 years	1	16
Wicker et al., 2003	fMRI (3 T)	14	20–27 years	2	26
Wiesmann et al., 2006	fMRI (1.5 T)	22	27 years/22–40 years	1	15
				10	119

al., 1998b, 2000), but also from passive stimulus presentation (Yousem et al., 1997). This feedback mechanism might also be applicable to intranasal trigeminal perception. In light of the well-documented fact that intranasal trigeminal stimuli induce apnea (Alvaro et al., 1992; Boushey and Richardson, 1973; Yavari et al., 1996), a sentinel mechanism in place to limit the inhalation of harmful chemicals, and the hypothesis proposed by Sobel and colleagues, we suggest that the cerebellar activation commonly observed in trigeminal neuroimaging studies is related to a feedback mechanism regulating intranasal airflow.

### 3.2. Activation of the common olfactory network by trigeminal stimuli

Significant ALE values were observed in the piriform cortex and adjoining orbitofrontal cortex, which are cortical regions known traditionally as olfactory areas (Gottfried, 2006; Sobel et al., 1998b; Zald and Pardo, 2000; Zatorre et al., 1992).

The piriform cortex is a heterogeneous region spanning parts of two lobes, frontal (anterior piriform cortex) and temporal (posterior piriform cortex) lobe, and is most commonly associated with olfactory processing (Zatorre et al., 1992). However, this meta-analysis revealed that stimulation with a painful dose of CO<sub>2</sub>, as opposed to an odorous stimulus, also resulted in high activation likelihood estimate values in the anterior portion of the piriform cortex. That said, we would like to stress that the spatial resolution of an ALE analysis is restricted by the width of the kernel used for spatial smoothing (10 mm) of the data. Although, the piriform cortex is considerably larger than our smoothing diameter, as for many functional imaging studies, the exact peak location can not be accurately localized to subsections within the piriform cortex with an absolute certainty. Four potential hypotheses could be postulated in respect of this finding. First, activation of the piriform cortex may be due to a subset of human olfactory receptors that respond to odorous and CO<sub>2</sub> stimulation alike. The possibility that CO<sub>2</sub> is not a pure trigeminal stimulus provides a second, though unlikely, hypothesis for trigeminal stimulation-derived cortical olfactory activations. Third, the finding is spurious in that it is mediated by potential differences in sniff characteristics. Fourth, the piriform cortex has a role in the integration of chemosensations, plausible due to the known strong behavioral links between the chemical senses.

Evidence supporting the first hypothesis, the existence of olfactory receptors responsive to CO<sub>2</sub>, comes from a range of

animal models, including bullfrogs (Coates and Ballam, 1990; Sakakibara, 1978), tegu lizards (Coates and Ballam, 1987), reptiles (Coates and Ballam, 1989), and mice (Hu et al., 2007). Furthermore it is possible that olfactory brain areas are activated during the perception of trigeminal CO<sub>2</sub> stimuli via trigeminal ganglion cells with sensory endings in the nasal epithelium that also send branches into the olfactory bulb and the spinal trigeminal complex which were discovered by Schaefer and colleagues (2002). It is worth pointing out that unequivocal evidence that CO<sub>2</sub> is not detected as an odor does not exist; this could be attributed to the fact that proving a negative result is a Sisyphus task. However, this gives rise to the second hypothesis. It is possible that activation in the piriform cortex is mediated by activity in the olfactory system, induced by CO<sub>2</sub> that is either not perceived as an odor per se or is below perceptual awareness. In other words, it is possible that a weak odorous sensation, originating from CO<sub>2</sub>, produces the demonstrated activation in the piriform cortex. However, since it is challenging to map olfactory evoked piriform cortex activation due to the inherent weak neuronal signal in the olfactory system (due to adaptation and habituation) and known artifacts in functional imaging studies (for review see Gottfried, 2006; Sobel et al., 2003) such weak odorous stimuli tend not to be detected as activation in the piriform cortex (e.g. Bensafi et al., 2008; Boyle et al., 2007; Dade et al., 2001; Kettenmann et al., 1996, 1997). In our view, the magnitudes of the activations elicited by CO<sub>2</sub> are far too large to be elicited by a sub-threshold odor.

The third hypothesis, activation of the piriform cortex due to sniffing, originates from two studies of Sobel and colleagues (1998a, 2000) demonstrating that activation in piriform cortex is induced in the presence or absence of an odorant just by the simple act of sniffing. However, as stated above, trigeminal stimuli induce apnea which would effectively lead to a marked reduction, rather than an increase in sniff frequency. The apnea inducing nature of the stimulus merged with the fact that the included studies were conducted using velopharyngeal closure (personal communication), thus specifically prevented them to breathe through their noses, renders it unlikely that the demonstrated piriform cortex activation is mediated due to the secondary act of sniffing.

Support for the fourth hypothesis, a role for the piriform cortex in chemosensory integration, is derived from an array of studies showing that independent of odor detection, the piriform cortex seems to process stimuli from all three chemical senses. Though the piriform cortex is often labeled as primary olfactory cortex, it is a heterogeneous area

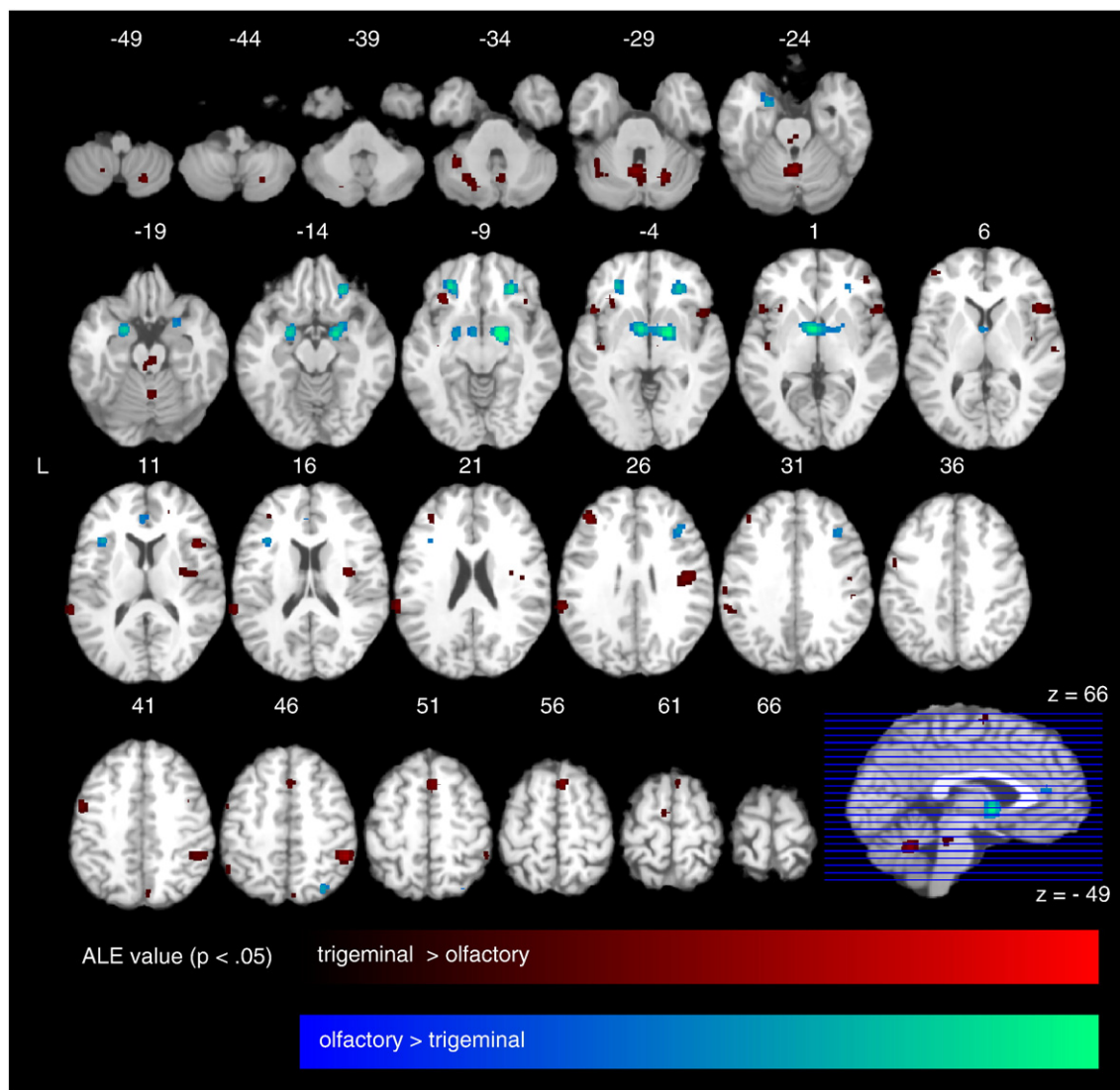
**Table 3 – Localization of significant FDR corrected ALE values due to intranasal trigeminal stimulation with CO<sub>2</sub> (contrast “CO<sub>2</sub> versus Baseline”).**

Cluster number	Cluster volume (mm <sup>3</sup> )	ALE (*10 <sup>-3</sup> )	Talairach coordinates			Brain area
			x	y	z	
1	4640	18.13	44	16	10	Frontal operculum
		12.34	46	10	-2	Frontal operculum
		12.13	38	20	-8	Basal operculum / Orbitofrontal cortex (OFC)
		11.85	36	6	-16	Dorsal temporopolar gyrus
		11.54	52	14	2	Frontal operculum
2	2408	10.23	36	8	2	Insula
		15.11	-38	36	28	Middle frontal gyrus
		11.89	-42	46	8	Middle frontal gyrus
3	1944	14.69	-62	-38	22	Superior temporal gyrus
		13.49	-62	-40	14	Superior temporal gyrus
4	1896	15.99	0	-58	-26	Cerebellum (declive)
		10.61	6	-64	-32	Cerebellum (pyramis)
5	1856	18.24	50	-44	46	Supramarginal gyrus
6	1672	14.01	-34	-52	-32	Cerebellum (declive)
		11.33	-24	-64	-32	Cerebellum (declive)
		10.84	-18	-72	-36	Cerebellum (crus I)
7	1560	16.96	-32	26	-8	Posterior orbital gyrus / Orbitofrontal cortex (OFC)
		11.34	-32	14	2	Insula
8	1336	13.11	44	-14	26	Postcentral gyrus / Primary somatosensory cortex (S I)
9	1272	15.00	6	16	54	Superior frontal gyrus
10	1240	13.41	32	-8	16	Insula
		10.97	40	-10	10	Frontal operculum/insula
11	696	12.71	-46	14	-2	Frontal operculum
12	688	12.41	-4	-6	62	Superior frontal gyrus
13	680	13.66	22	-64	-28	Cerebellum (declive)
14	616	12.94	-58	-24	32	Parietal operculum / Secondary somatosensory cortex (S II)
15	584	11.40	-50	-2	40	Precentral gyrus
16	552	11.10	4	-28	-20	Mesencephalic trigeminal nucleus (brainstem)
17	520	10.04	-40	-16	-2	Insula
		8.94	-32	-14	-10	Ventral putamen
18	512	11.34	-38	-2	-10	Insula
19	472	10.57	46	2	50	Middle frontal gyrus
20	448	10.24	20	42	8	Superior frontal gyrus
21	384	12.65	22	-66	-46	Cerebellum (pyramis)
22	368	12.07	20	8	-10	Piriform cortex
23	288	10.53	6	-76	42	Superior parietal lobule
24	240	10.21	2	32	22	Anterior cingulate gyrus
25	200	10.17	12	-16	10	Ventrolateral posterior thalamic nucleus
26	152	9.47	8	-14	-6	Mammillo-thalamic tract
27	144	9.38	42	40	0	Inferior frontal gyrus (orbital part)
28	136	8.95	50	-28	30	Parietal operculum / Secondary somatosensory cortex (S II)
29	104	8.52	-48	-54	46	Supramarginal gyrus

Significant activation clusters are reported together with stereotaxic coordinates with regard to [Talairach and Tournoux \(1988\)](#), cluster volume, and activation likelihood estimation of the local activation maximum.

proposed to respond in several higher order olfactory tasks, such as odor memory ([Dade et al., 2002](#)) and attention to odors ([Zelano et al., 2005](#)), as well as during odor imagery ([Bensafi et al., 2007](#); [Gonzalez et al., 2006](#)). Efforts have recently been made to discriminate amongst primary olfactory processes mediated by the anterior and posterior piriform cortex. [Gottfried and colleagues](#) postulated that activation of the anterior piriform cortex corresponds to perception of an odor stimulus per se,

whereas posterior piriform cortex activity is related to the quality of a chemosensory percept ([Gottfried et al., 2006](#); [Howard et al., 2009](#); but see also [Gottfried et al., 2002](#)). Additional evidence for activation of the anterior piriform cortex driven by odor detection has been published by [Zelano and colleagues \(2005\)](#). However, it is interesting to note that activations in the piriform cortex have also been reported in imaging studies investigating the cortical processing of taste



**Fig. 2 – Localization of significant FDR corrected ( $p < .05$ ) ALE values exclusively related to trigeminal stimulation (trigeminal > olfactory) and olfactory stimulation (olfactory > trigeminal) projected onto the standard template in Talairach space ( $z = -49$  to  $66$ , L = left). Red colors represent trigeminal ALE results whereas blue colors represent olfactory ALE values.**

stimuli (Small et al., 1997). In other words, the piriform cortex seems to process chemosensory stimuli from all the three chemical senses independent of whether or not an odor is detected. Based on this, we support the hypothesis that the piriform cortex is a chemosensory integration area. More evidence supporting the fourth hypothesis, an integrative role of the piriform cortex in chemosensory processing, comes from fMRI studies aimed at mapping the cerebral processing of odors with both trigeminal and olfactory percepts, commonly known as bimodal odors (Albrecht et al., 2007, 2009). Bimodal odorants typically evoke odor perceptions at low concentrations and burning or stinging sensations at higher concentrations, thus enabling the separation of trigeminal from olfactory processing. Stimulated with low concentrations of a bimodal odorant, subjects reported no trigeminal sensations despite clear activity in both the olfactory and the trigeminal

neuronal systems were located, thus lending further support to the notion that the sensory systems within the nose might interact based on stimulus location rather than sensory system belonging. This integrational function could arise from the repetitive and complex paired association that our everyday percept of flavor is provoking, a complex interaction between odorous, trigeminal, and gustatory sensation.

### 3.3. Comparison of networks responsible for processing of olfactory and trigeminal stimuli

A comparison of the olfactory and trigeminal ALE maps displays a clear overlap of the two chemosensory networks, especially in the right piriform cortex, insula, and middle frontal gyrus, as well as in a minor portion of the orbitofrontal cortex. These areas are well-known members of the network processing

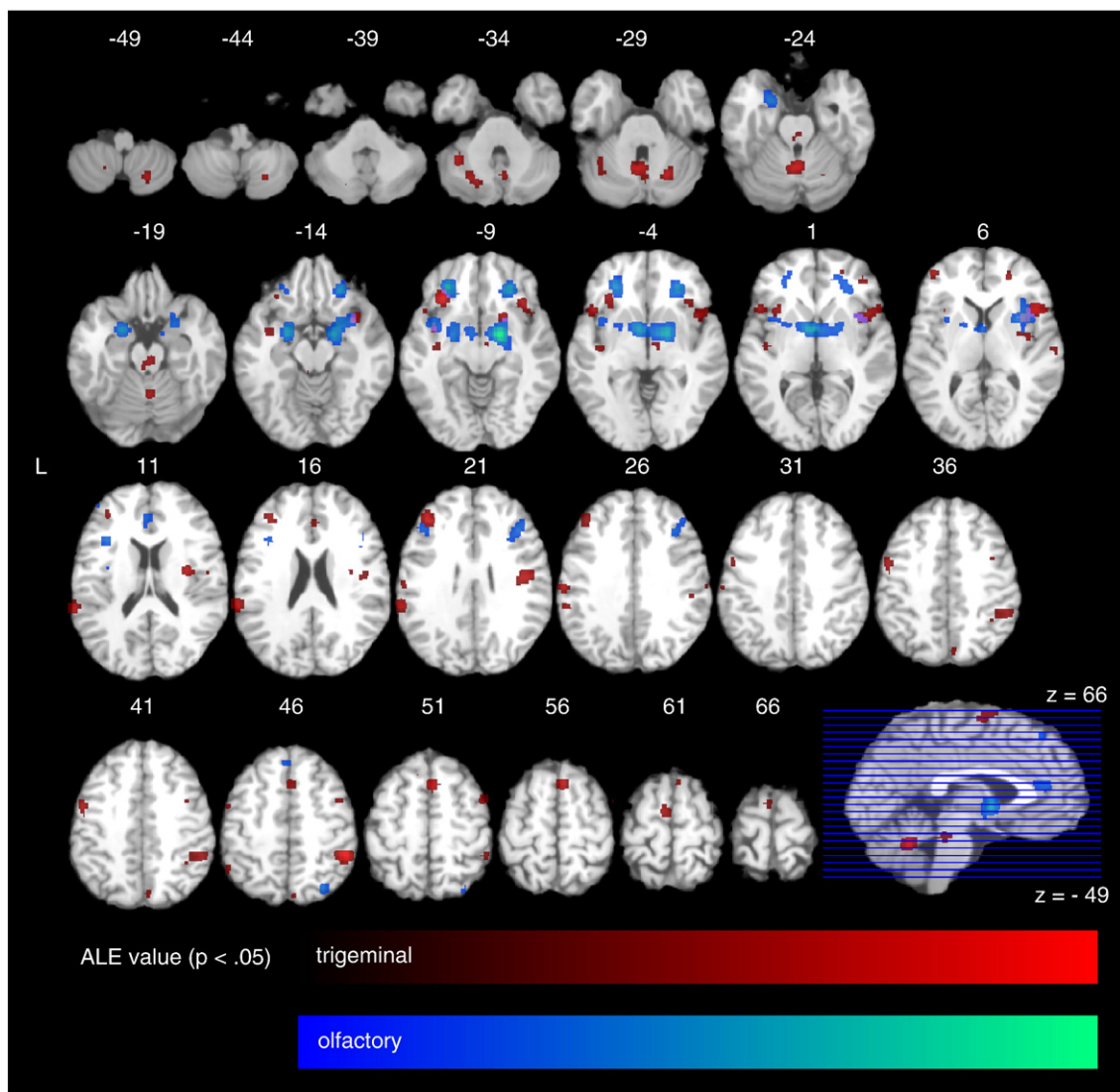
**Table 4 – Localization of significant FDR corrected ALE values: (a) trigeminal stimulation (trigeminal > olfactory); (b) olfactory stimulation (olfactory > trigeminal).**

Cluster number	Cluster volume (mm <sup>3</sup> )	ALE (*10 <sup>-3</sup> )	Talairach coordinates			Brain area
			x	y	z	
<i>(a) Trigeminal &gt; olfactory</i>						
1	2040	15.99	0	-58	-26	Cerebellum (declive)
		10.61	6	-64	-32	Cerebellum (pyramis)
2	1856	16.79	44	16	10	Frontal operculum
		11.40	52	14	2	Frontal operculum
		10.99	46	12	-4	Frontal operculum
3	1776	14.32	-62	-38	22	Superior temporal gyrus
		12.96	-62	-40	14	Superior temporal gyrus
4	1744	14.00	-34	-52	-32	Cerebellum (declive)
		11.32	-24	-64	-32	Cerebellum (declive)
		10.84	-18	-72	-36	Cerebellum (crus I)
5	1736	18.24	50	-44	46	Supramarginal gyrus
6	1384	13.11	44	-14	26	Postcentral gyrus / Primary somatosensory cortex (S I)
7	1248	15.00	6	16	54	Superior frontal gyrus
8	1160	14.54	-38	36	28	Middle frontal gyrus
9	832	13.14	32	-8	16	Insula
		10.33	40	-10	10	Frontal operculum/Insula
10	752	14.98	-32	24	-8	Posterior orbital gyrus / Orbitofrontal cortex (OFC)
		9.08	-32	16	2	Insula
11	664	13.66	22	-64	-28	Cerebellum (declive)
12	624	11.40	-50	-2	40	Precentral gyrus
13	480	10.72	4	-28	-20	Mesencephalic trigeminal nucleus (brainstem)
14	456	12.16	-46	14	-4	Frontal operculum
15	336	12.65	22	-66	-46	Cerebellum (pyramis)
16	296	10.64	-4	-8	62	Superior frontal gyrus
17	256	10.53	6	-76	42	Superior parietal lobule
18	224	10.02	-40	-16	-2	Insula
19	208	10.44	-42	46	6	Middle frontal gyrus
20	152	8.52	-48	-54	46	Supramarginal gyrus
21	128	9.36	42	40	0	Inferior frontal gyrus (orbital part)
22	112	9.26	-60	-24	32	Parietal operculum / Secondary somatosensory cortex (S II)
<i>(b) Olfactory &gt; trigeminal</i>						
1	5712	18.05	-6	-2	-2	Thalamus
		28.21	18	-6	-8	Amygdala
2	1880	15.92	-20	-4	-14	Amygdala
3	1864	18.33	24	32	-10	Posterior orbital gyrus
4	1128	16.41	-24	34	-8	Posterior orbital gyrus
5	624	11.46	38	26	28	Middle frontal gyrus
6	456	12.33	-36	18	14	Frontal operculum
7	384	12.49	30	-72	48	Parietal occipital transition area
8	208	9.88	-2	36	14	Anterior cingulate gyrus

Significant activation clusters are reported together with stereotaxic coordinates with regard to [Talairach and Tournoux \(1988\)](#), cluster volume, and activation likelihood estimation of the local activation maximum.

trigeminal stimuli, mentioned above, and of the network processing olfactory stimuli (for review see [Gottfried, 2006](#)). However, the comparison also reveals areas that are specifically activated by either the trigeminal irritant (CO<sub>2</sub>) or by odorous stimuli. Although defining the peak ALE cluster scores to exact subdivisions of the various cortical regions is not an exact science due to the filters used and variation between subject and studies, one can see in [Fig. 4](#) that trigeminal and olfactory stimuli activate common areas but peak ALE scores are mostly separated within each gross anatomical division. If one studies the individual subdivisions of piriform cortex and orbitofrontal

cortex one can find an interesting pattern. Trigeminal stimuli activate the anterior piriform cortex and the posterior orbitofrontal cortex (within area 131), whereas olfactory stimuli render the highest ALE values in the posterior piriform cortex and the anterior orbitofrontal cortex (within area 13m). Both piriform and orbitofrontal cortex are connected to the somatosensory system via afferent inputs from SII ([Saleem et al., 2008](#)). This demonstrates the large degree of interconnectivity within the flavor processing network and lends further support to the view that the three chemical senses are not isolated networks. Future studies seeking to distinguish olfactory from trigeminal



**Fig. 3 – Localization of significant FDR corrected ( $p < .05$ ) ALE values that overlap with regard to intranasal trigeminal and olfactory stimulation (10 contrasts each) projected onto the standard template in Talairach space ( $z = -49$  to 66, L=left). Red colors represent trigeminal ALE results, purple colors represent the overlap in ALE values and blue colors represent olfactory ALE values.**

functional networks should map and label activation within subregions rather than gross anatomical regions.

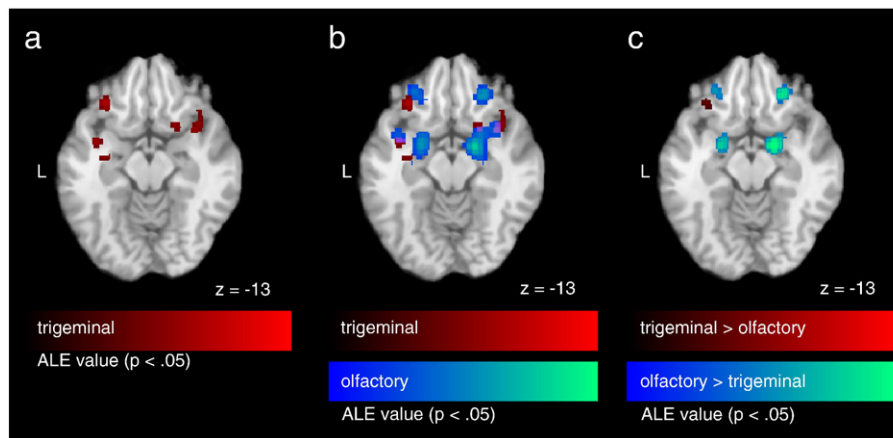
#### 3.4. Overall conclusion

With the help of the meta-analytical tool ALE, we provide an *in vivo* detailed mapping of human brain areas responsive to intranasal trigeminal stimulation. In addition, our results demonstrate that both the trigeminal and olfactory systems are consistently activated with a high probabilistic certainty during perception of a pure trigeminal substance and illustrate significant activation overlaps within the piriform cortex. These system interactions demonstrate that only when we understand the integration of olfactory, gustatory, and trigeminal network processing can we start to fully understand how we process food and flavor.

## 4. Experimental procedures

### 4.1. Identification of publications

Different data sources were used for identification of publications using functional neuroimaging methods to investigate the neuronal processing of intranasal trigeminal stimulation. We searched for publications using the online citation index service (Medline) and the keywords “intranasal trigeminal fMRI” and “intranasal trigeminal PET” (including acronyms and synonyms like “intranasal pain”, “functional resonance imaging”, “positron emission tomography”). We utilized publications published before 1 March 2009 and analyzed the reference lists of these publications to find additional articles. Due to the limited number of published studies, we opted to



**Fig. 4** – Significant FDR corrected ( $p < .05$ ) ALE values in piriform cortex which (a) are caused by intranasal stimulation with  $\text{CO}_2$  (contrast “ $\text{CO}_2$  versus Baseline”), (b) overlap with regard to trigeminal and olfactory stimulation (10 contrasts each, olfactory + trigeminal), and (c) differ with regard to trigeminal and olfactory stimulation (trigeminal > olfactory, olfactory > trigeminal). Significant ALE values ( $p < .05$ ) are projected onto a standard template (colin1.1.nii) in Talairach space (L=left). The piriform cortex activation is shown on a selected axial slice ( $z = -13$ ). Red colors represent trigeminal or trigeminal > olfactory ALE values, purple colors represent the overlap in ALE values (olfactory + trigeminal), blue colors represent olfactory or olfactory > trigeminal ALE values.

include the datasets of one submitted (Schoepf et al., 2009) and three unpublished studies from our group. Regarding the unpublished studies, the first experiment was aimed at investigating cerebral activation in response to a low concentration of  $\text{CO}_2$ , the second experiment was aimed at investigating cerebral activation in response to a high  $\text{CO}_2$  concentration, and the third experiment explored cerebral activation due to different concentrations of  $\text{CO}_2$  stimuli. The methods and results of the unpublished studies are described in detail in the [Supplementary Materials](#).

#### 4.2. Inclusion criteria

The following inclusion criteria were applied to the identified publications: (1) use of functional imaging methods (fMRI/PET) to investigate brain activation following mere intranasal stimulation with  $\text{CO}_2$ ; (2) results of a whole brain volume or small volume correction analysis; (3) 3D coordinate-based data ( $x, y, z$ ) reported in standardized stereotactic space (Montreal Neurological Institute (MNI) or Talairach); (4) results for a group of healthy subjects; (5) results originating from a main  $\text{CO}_2$  contrast ( $\text{CO}_2$  versus Baseline). Contrasts meeting these criteria were included regardless of tasks during or after scanning. We opted to use a less stringent task-specific inclusion criterion since the ALE methodology identifies brain activations that are unrelated to the processing of intranasal  $\text{CO}_2$  stimulation due to their inconsistent activation pattern across studies.

#### 4.3. Activation likelihood estimations (ALE)

The original ALE meta-analysis algorithm was developed by Turkeltaub et al. (2002) and was recently modified by Laird and colleagues (2005) to include the possibility of a correction for multiple comparisons, the comparison of two different ALE analyses, and an automatic meta-analysis in Talairach space.

Detailed descriptions of the ALE algorithm can be found in Turkeltaub et al. (2002) and Laird et al. (2005), and these algorithms are implemented in BrainMap (BrainMap GingerALE 1.1, <http://brainmap.org/ale>). During standard analysis of neuroimaging data, functional images are spatially normalized to a stereotactic template that might differ between studies. These anatomical templates are not directly comparable due to minor anatomical deviances. Therefore, in order to facilitate comparisons, all data included in the statistical meta-analysis were transformed into Talairach space, the template supported by the ALE software. After transformation into Talairach space, all coordinates were imported into the Java-based version of the ALE software and analyzed using a fully automated procedure.

A whole-brain ALE map was created by dividing the Talairach space into  $8 \text{ mm}^3$  voxels and modelling a Gaussian probability distribution centered at each reported activation coordinate. A voxel-wise calculation of the probability that each focus was located within that particular voxel was then performed using a 3D Gaussian function with a 10 mm FWHM (full-width, half-maximum) filter. Subsequent non-parametric permutation tests ( $n = 7000$ ) were used to test the null hypothesis that activation foci are distributed uniformly across the brain. Resulting statistical maps were corrected for multiple comparisons utilizing the false discovery rates (FDR) (Genovese et al., 2002; Laird et al., 2005) at a level of  $p < 0.05$  and a minimal cluster volume of  $100 \text{ mm}^3$ .

In order to compare ALE values due to trigeminal and olfactory stimulation, we created a whole-brain ALE map for olfactory stimulation by using an automated randomization algorithm to select studies from the pool of studies used for an ALE meta-analysis of olfactory functional brain imaging data (Lundstrom and Djordjevic, 2009). All studies included in the olfactory ALE meta-analysis utilized a main olfactory contrast (olfactory stimulation versus baseline). The algorithm matched the number of included contrasts ( $n = 10$ ) and assured that these contrasts originated from the same ratio of fMRI and

PET methodology (9 fMRI contrasts, 1 PET contrast). To keep the structure of the obtained data we used only whole experimental datasets instead of including random contrasts. The olfactory ALE map was created using the methods described above for the trigeminal ALE map.

The two ALE maps (trigeminal and olfactory) were compared by creating an additional ALE map of voxels in which there is a statistical difference in likelihood of activation by stimulation with the two modalities. Both lists of foci were loaded into the ALE software (BrainMap GingerALE 1.1, <http://brainmap.org/ale>), one as the main foci list (trigeminal stimulation) and one as the subtraction foci list (olfactory stimulation). These two datasets were then statistically compared for convergences as described in detail elsewhere (Laird et al., 2005). Briefly, the main difference from the procedure described above is that after the probability is calculated in each voxel for both groups, the obtained ALE values are subtracted between groups rendering a measure of inter-map convergence for each voxel. A statistical measure of the level of convergence is then obtained by the methods and settings described above. This was performed for each contrast [(trigeminal>olfactory), (olfactory>trigeminal)].

For visualization purposes, the anatomical template provided on the Ginger ALE website (colin1.1.nii, Kochunov et al. (2002), <http://brainmap.org/ale>) was overlaid with the different thresholded ALE maps using MRICron (version beta 31, <http://www.sph.sc.edu/comd/rorden/mricron/>). To visualize overlaps between olfactory and trigeminal stimulation, the olfactory ALE map was superimposed on the trigeminal ALE map. To visualize differences in the ALE maps the trigeminal>olfactory ALE map was superimposed on the olfactory>trigeminal ALE map. Local maxima of activation clusters were labeled using an anatomical atlas (Mai et al., 2004) and cross-checked using MRICron. Subdivisions of the OFC were labeled using architectonic maps from within Carmichael and Price (1994).

## Acknowledgments

This work was supported by the National Institute on Deafness and other Communication Disorders (NIDCD R03DC009869) awarded to JNL and a fellowship within the postdoctoral program of the German Academic Exchange Service (DAAD) awarded to JA. We are grateful to Amy R. Gordon for proofreading the manuscript.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.brainresrev.2009.11.001](https://doi.org/10.1016/j.brainresrev.2009.11.001).

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