Neural Basis of Olfactory and Trigeminal Integration

Abbreviated title: Olfactory-trigeminal neural integration

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ABSTRACT

Humans naturally integrate signals from the olfactory and intranasal trigeminal systems. A tight interplay has been demonstrated between these two systems, and yet the underlying neural circuitry that mediate olfactory-trigeminal integration remains unclear. Using functional magnetic resonance imaging (fMRI), this study investigated the neural mechanisms underlying olfactory-trigeminal integration. Fifteen subjects with normal olfactory function performed a localization task with weak or strong air-puff stimuli, phenylethyl alcohol (PEA; rose odor), or a combination. Although the ability to localize PEA to either nostril was at chance, its presence significantly improved the localization accuracy of weak, but not strong, air-puffs, relative to the localization of air-puffs without concomitant PEA, when both stimuli were delivered concurrently to the same nostril. This enhancement in localization accuracy was directly correlated with the magnitude of multisensory activity in the primary olfactory cortex (POC). Changes in orbitofrontal cortex (OFC) multisensory activity alone could not predict task performance, but changes in OFC *and* POC connectivity could. Similar activity and connectivity patterns were observed in the superior temporal cortex (STC), inferior parietal cortex (IPC) and the cerebellum. Taken together, these results suggest that olfactory-trigeminal integration is occurring across multiple brain regions. These findings can be interpreted as an indication that the POC is part of a distributed brain network that mediate the integration between olfactory and trigeminal systems.

1. INTRODUCTION

Olfactory and intranasal trigeminal systems convey complementary information that are merged via mutually enhancing and/or suppressing interactions [1, 2]. For example, the trigeminal component of an odorant (at least in higher concentrations) has been shown to reduce how humans perceive the olfactory content of odors [3, 4]. Conversely, trigeminal stimuli are perceived as more intense in the presence of olfactory co-stimulation [5, 6]. Thus, perceptual judgements in either the olfactory or trigeminal modality partly reflect the combined effects of both systems. These observations support the premise that the olfactory and intranasal trigeminal systems work in tandem [2].

The ophthalmic and maxillary branches of the trigeminal nerve are known to innervate the nasal cavity [7]. Touch, pressure, temperature, and nociception are mediated by trigeminal afferents, with different sensory receptors mediating different sensations [8, 9].These trigeminal sensations are categorized into either chemosensory or somatosensory domains, although they are all processed via the same trigeminal nerve. The central sensory pathways of these two domains; however, seem to be relatively independent from each other [10]. In contrast, olfactory information is independently processed via the first cranial nerve. Since most odorants stimulate both cranial nerves, mutual interactions between the two systems are known to take place across multiple processing levels [1, 2, 11].

Sensory integration improves detection, discrimination and categorization of stimuli, conferring evolutionary advantages to animals and humans in understanding, navigating, and perceiving the environment [12] . In the traditional hierarchical view, integration is deferred until *after* extensive 'unisensory' processing [13, 14]. The superior temporal sulcus (STS) [15], lateral occipital–temporal cortex [16], posterior parietal cortex (IPC) [17], and ventrolateral frontal cortex [18] have all been identified as brain regions where multisensory information converge. Interestingly, recent results suggest a different perspective on multisensory integration, wherein

this process is supported by a distributed neural network that includes both primary sensory cortices as well as higher-order multisensory brain regions [19, 20].

The olfactory system is often considered an underdetermined human sense [21, 22]. Multisensory integration; therefore, imparts substantial benefits to olfactory processing [23], e.g., the absence of pertinent visual information is known to impede odor identification [22]. Similarly, adding a pure trigeminal stimulus to varying concentrations of an odorant modulated the perceived intensity of the odor [5]. Furthermore, trigeminal perception is significantly impaired in subjects with anosmia [24]. Taken together, these observations allude to a tight coupling between the olfactory and trigeminal systems, and yet the underlying mechanisms of these interactions remain largely unknown [25-29]

The intranasal trigeminal system has been investigated using localization tasks in which participants have to identify the stimulated nostril [30-32]. These tasks capitalize on the fact that an odorant can *only* be localized to a nostril if that odorant also stimulates the trigeminal nerve [30]. Thus, localization tasks are ideal for dissociating the perceptual contributions of trigeminal and olfactory stimuli. These studies have shown that humans can localize trigeminal and bimodal (olfactory and trigeminal) stimuli, but they cannot localize pure odorants that *only* activate the olfactory nerve [30, 33-35].

Olfactory processing encompasses both sniffing and smelling [36, 37]. Sniffing is typically active, but passive sniffing is a useful laboratory task that allows precise stimulus control and avoids the confounds of enhanced odorant delivery due to increased airflow. During passive sniffing, an odorant is delivered into participants' nostrils using air-puffs: both active and passive sniffing improve olfactory perception [33]. During active sniffing, the olfactory system estimates airflow rates in both nostrils using the motor action of sniffing and somatosensory stimulation from airflow. Sobel et al. (1998) reported sniff-induced activation in the primary olfactory cortex (POC) as a result of somatosensory airflow-induced stimulation, as opposed to the purely motor action of sniffing. Thus, air-puff induced stimulation is closely related to the somatosensory

component of sniffing behavior, which is considered an integral part of the olfactory percept [36, 37]. Although less studied, olfactory information has been shown to influence an intranasal trigeminal percept; olfactory co-stimulation in the same nostril has also been shown to enhance the localizability of intranasal trigeminal (chemosensory) stimuli [26]. To our knowledge, the effects of olfactory co-stimulation have not been studied for intranasal somatosensory stimuli.

During passive sniffing, the intranasal trigeminal system is stimulated by changes in airflow, indicating possible pressure changes. The present study used a psychophysical approach to investigate the effects of a pure odorant, phenyl ethyl alcohol (PEA; rose odor), which cannot itself be localized to one or another nostril above chance, on the localizability of intranasal somatosensory stimuli (air-puffs). We hypothesized that multisensory integration would occur for the combination of somatosensory and olfactory stimuli, predicting that PEA would enhance the localizability of weak, but not strong air-puffs, conforming to the well-known principle of inverse effectiveness in multisensory integration [38], i.e., integration occurs for weak, but not strong stimuli. Furthermore, we predicted that PEA would enhance the localizability of weak air-puffs only when both kinds of stimuli were presented to the same nostril, and not when PEA and air-puffs were presented to opposite nostrils in accordance with the spatial principle of multisensory integration [39], i.e., integration occurs for spatially concordant but not discordant stimuli. We employed functional magnetic resonance imaging (fMRI) to examine the neural basis of these multisensory interactions. Data from rodents [20], non-human primates [40], and humans [22] suggests that cross-modal stimulation is capable of modulating activity in the POC. This brain structure receives extensive reciprocal projections from other olfactory and higher-order brain regions, such as the orbitofrontal cortex (OFC) - a critical site for multisensory integration for the olfactory system [41]. We; therefore, tested the hypothesis that olfactory-trigeminal integration is supported by multisensory interaction in the POC (as in other primary sensory cortices) [13]. It has been suggested that sensory convergence in primary sensory cortices may be mediated by higher-order multisensory brain regions [42]. We also tested the hypothesis

that multisensory effects in the OFC, STS and posterior parietal cortex (known higher-order multisensory brain regions) contribute to olfactory-trigeminal integration. Lastly, we tested the hypothesis that the effects of multisensory interaction in the POC is, in fact, *driven* by its connectivity with the OFC, STS and IPC.

2. METHODS

2. 1. Participants

Fifteen subjects (mean age: 27.20 ± 5.07 years, 11 females and 4 males) took part in the fMRI experiments. Their smell function was evaluated using the University of Pennsylvania Smell Identification Test (UPSIT) [43] and the OLFACT [44, 45]. UPSIT tests an individual's ability to detect and identify suprathreshold odorants using 4 different 10-page booklets: 40 questions total. There is a "scratch and sniff" strip on each page that needs to be identified given four multiple choices. OLFACT is a test battery that evaluates odor-identification and odor-threshold abilities using a computer-based system. The study had prior approval from the Pennsylvania State University College of Medicine Institutional Review Board (IRB). Participants (recruited from south-central Pennsylvania) provided informed consent and were screened to rule out (i) MRI incompatibility; (ii) any neurological or psychiatric conditions and (iii) disorders that could specifically cause olfactory dysfunction, such as viral infections and allergies.

2. 2. Imaging Protocol

The fMRI experiment consisted of four runs: two runs each for weak and strong air-puff experiments. These experiments were pseudorandomized and counterbalanced across subjects. The total scan time of the fMRI experiments was 25 mins. fMRI images of the entire brain were acquired using GE EPI on a Siemens Prima 3.0 T system with a 20-channel head coil. The following imaging parameters were used: repetition time/echo time/flip angle (TR/TE/FA) = 2,000 ms/30 ms/90°; field of view (FOV) = 220 mm x 220 mm; acquisition matrix = 80 x 80, 34 slices; slice thickness = 4 mm, and the number of repetitions = 240. For the anatomical overlay, T1-weighted images with 1 mm isotropic resolution were acquired with the magnetization-prepared, rapid gradient echo (MPRAGE) method: TE = 2.98 ms; TR = 2300 ms; inversion time = 900 ms; FA = 9°; FOV = 256 mm × 256 mm × 160 mm; acquisition matrix = 256 × 256 × 160; acceleration factor = 2.

2.3. Experimental design

The study utilized a two-alternative forced-choice (2AFC) paradigm. The structure of the

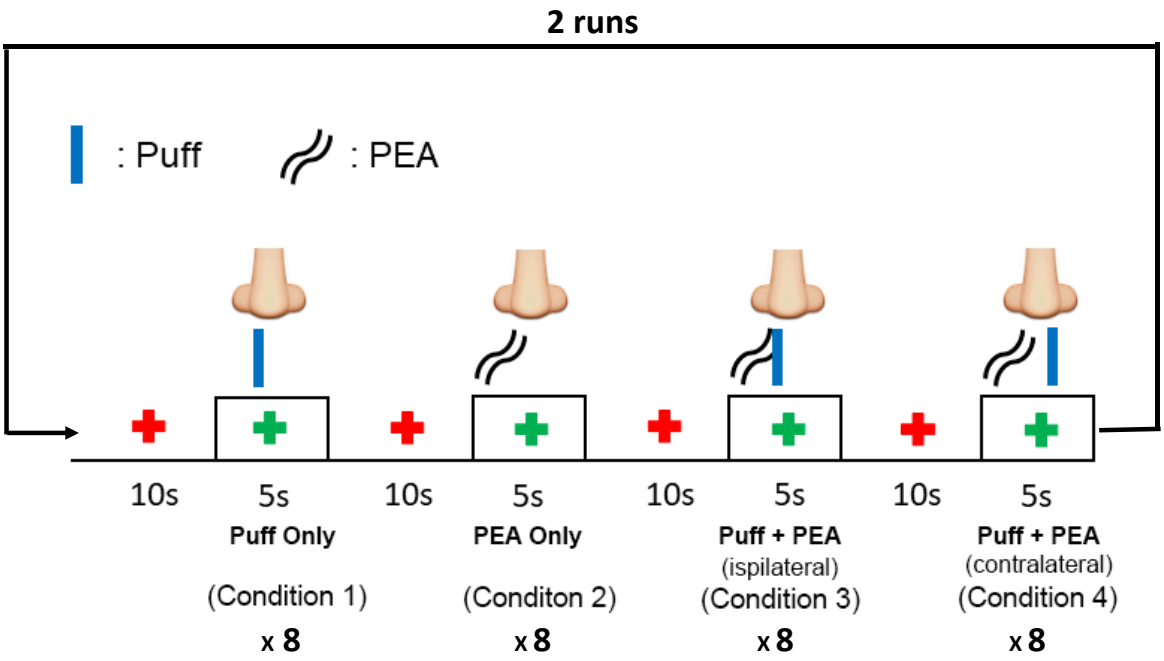

Figure 1. *Air-puffs with a flow rate of 2L/min(weak) or 4L/min(strong), and/or pure odorant stimuli (PEA): 100 ms for each stimulus, were randomly delivered to either the left or right nostrils, with an inter-stimulus interval of 10 s. Participants were instructed to focus on a red 'fixation cross' that appeared on screen. When the cross turned green, they were instructed to hold their breath for 5 s and attend to the stimulus, which lasted 100ms. Subjects provided responses by indicating which nostril was stimulated (*or the side of stimulation). *Responses were recorded with the olfactometer. This paradigm structure is the same for weak and strong air puff experiments.*

paradigm, in terms of event timings, is shown in **Figure 1**. There were four runs comprised of two types of experiments: two runs with weak air-puffs (airflow of 2L/min) and the other two with strong air-puffs (airflow of 4L/min) [see **Figure 1**]. For each run, there were four experimental conditions presented pseudo-randomly: 8 trials for each condition—totaling 32 trials for a single

run (1 of 4 total runs). All runs = 128 trials evenly distributed amongst four conditions. Condition 2: PEA (2-phenylethyl alcohol; Sigma # 77861) was presented alone, without air-puffs, and subjects were asked to localize it; Condition 1, air-puffs were presented alone and subjects were asked to localize them. In each of these two conditions, stimuli alternated randomly between nostrils. The third and fourth conditions comprised bisensory stimulation with both air-puffs *and* PEA. Condition 3: both stimuli were randomly presented to the same nostril (ipsilateral); Condition 4: both stimuli were presented to opposite nostrils (contralateral). For condition 4, air puff and PEA were always delivered to opposite nostrils. Stimuli alternated randomly between nostrils in conditions 3 (air puff+PEA to same nostril) and 4 (air puff to left and PEA to right, or vice versa). For the weak and strong experiments, subjects were asked to localize the side of stimulation, whether it be an air-puff or PEA. The inter-stimulus interval (ISI) was approximately 10 sec (red cross), without counting the breath-holding period; in all experiments, the stimulus duration was always 100ms embedded within a 5 s "breath-holding" period (green cross). We carefully selected the ISI and the total experiment time to avoid desensitization during the testing period [46]. Five to ten minute pauses between runs were incorporated to ensure that participants were not tired and that their sensory perception remained unaltered. Visual cues were used to inform subjects to hold their breath, and to localize the stimulated nostril. In respective experiments, air-puffs were embedded in a constant flow of odorless air, delivered bilaterally at a rate of 2 L/min or 4 L/min, via an olfactometer.

2. 4. Data Analysis

2.4.1. fMRI Data Processing

The fMRI data was processed using SPM 12 software (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) . In brief, images were realigned within each run; they were slice timing corrected and spatially normalized to the Montreal Neurological Institute's (MNI) EPI brain template [47, 48]. These normalized images were smoothed with an

8×8×8 mm^3 (full width at half maximum, FWHM) 3D-Gaussian smoothing kernel. Statistical parametric maps were then generated for each subject, and for each condition, by fitting the paradigm time course, convolved with the canonical hemodynamic response function (HRF) and its time derivatives to the imaging data. One-sample t-tests were conducted to generate group activation maps. Following Beauchamp et al. (2005), multisensory interactions were investigated using a balanced contrast that required the multisensory response to be larger than the mean of the unisensory responses. In SPM, it was implemented using the contrast [-1, -1, 2] (puff, PEA, combination). Statistical inferences were performed at the voxel level with an FDR (False Discovery Rate) correction for multiple comparisons ($p < 0.05$) using AFNI software (https://afni.nimh.nih.gov/).

Statistical analyses were performed using SPSS (IBM SPSS Statistics). We first performed one-sample t-tests to determine whether the localization accuracy for each condition was greater than chance. We then used repeated-measures analysis of variance (ANOVA) to compare localization accuracies between conditions, followed by paired t-tests for post hoc comparisons. Bonferroni corrections for multiple comparisons were applied on an as needed basis at a set alpha value of 0.05 .

2.4.2. Brain connectivity analysis

The generalized form of the psycho-physiological interaction (gPPI) model was used to separately test for connectivity changes between brain regions that potentially mediate multisensory effects [49]. For each analysis, the seed region was defined by the group-level activation maps, with the threshold set to $p<0.05$, FDR corrected. For each seed region analysis: we first specified PPI models at the subject level using normalized, smoothed, functional EPI images as the data; condition-specific onset times for each run as the 'psychological' factor, and the first eigenvariate of seed region activation as the 'physiological' factor. These models also included nuisance

regressors for the run-wise, motion-correction parameters. Estimated connectivity parameters were entered into group level, one-sample t-tests.

3. RESULTS

3.1. Behavioral improvements

All study participants were normosmic (**Table 1**), and completed the weak and strong air-puff localization experiments inside the MRI scanner as shown in **Figure 1**.

Table 1. *Olfactory test scores of the study population*

	Olfact		UPSIT
	Threshold	***Identification***	***Identification***
Mean ± SD	11.73 ± 1.56	17.73 ±1.33	36.27 ± 1.75
Normal Range	>=8	>=16 (Total 20)	>=34(Total 40)

Figure 2 shows localization accuracy for weak air-puffs alone, which was comparable to that of PEA alone, being below 75% correct (usually taken as the threshold in a 2-AFC). There was a significant improvement in localization accuracy for weak air-puffs during PEA co-stimulation, indicating a significant enhancement in detection sensitivity when in the presence of PEA. However, this improvement was observed only when both stimuli were delivered to the same nostril. No such improvements in localization accuracy were observed when weak air-puffs and PEA were concurrently delivered to opposite nostrils. These results suggest that the olfactory-trigeminal interaction observed here fits with the spatial principle of multisensory integration. In contrast to these findings with weak air-puffs, strong air-puffs (which could be localized with suprathreshold accuracy in the absence of PEA) showed no significant improvement in localization accuracy when in the presence of PEA (**Figure 2B**), whether it was presented to the same or opposite nostril. Note: localization accuracy for strong air-puffs without PEA was well below ceiling, indicating that the lack of significant improvement with PEA was probably not due to a ceiling effect. These results also suggest that olfactory-trigeminal interactions conform to the principle of inverse effectiveness [50-52]. These same in-magnet results were previously replicated in an out-of-magnet behavioral experiment [53].

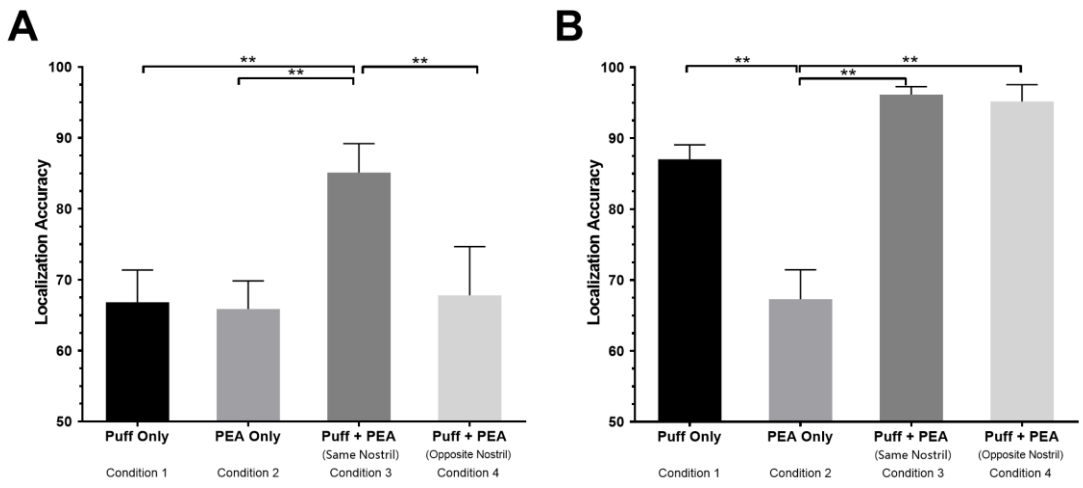

Figure 2. ***(A)*** *Localization accuracy for weak air-puffs significantly improved when PEA was presented to the same nostril (paired t-test, **p < 0.001), but not the opposite nostril.* ***(B)*** *Strong air-puffs were localized much better than weak air-puffs, but no significant improvement was observed with PEA co-stimulation. This was the case, whether PEA was in the same or opposite nostrils. Taken together, these results support the* ***principle of inverse effectiveness*** *during olfactory-trigeminal integration [38].*

3.2. Multisensory effects during olfactory-trigeminal interaction

In order to clarify and establish the loci of multisensory integration and their underlying neural mechanisms, we first analyzed fMRI data from the weak air-puff section of the experiment. Previous studies have suggested that merging olfactory and trigeminal information could be mediated via integrative mechanisms involving several brain regions; thus, we set out to optimize sensitivity to fMRI activity patterns using a balanced contrast criterion to delineate the multisensory effects in the brain. It should be noted that super-additivity requires that the multisensory response be larger than their summed unisensory responses. Beauchamp et al. (2005) showed that this criterion failed to classify the STS as a multisensory region in fMRI

studies, though there is a wealth of evidence suggesting that this region is merging multisensory information [54]. Using the less stringent criterion, that the multisensory response is larger than the maximum or the mean of their unisensory responses: STS was classified as multisensory. Following this empirical demonstration [55], we opted to use the latter criterion to delineate multisensory effects during olfactory-trigeminal interaction. The univariate analysis shown in **Figure 3** identified several brain regions that preferentially responded to a combination of olfactory and somatosensory stimuli.

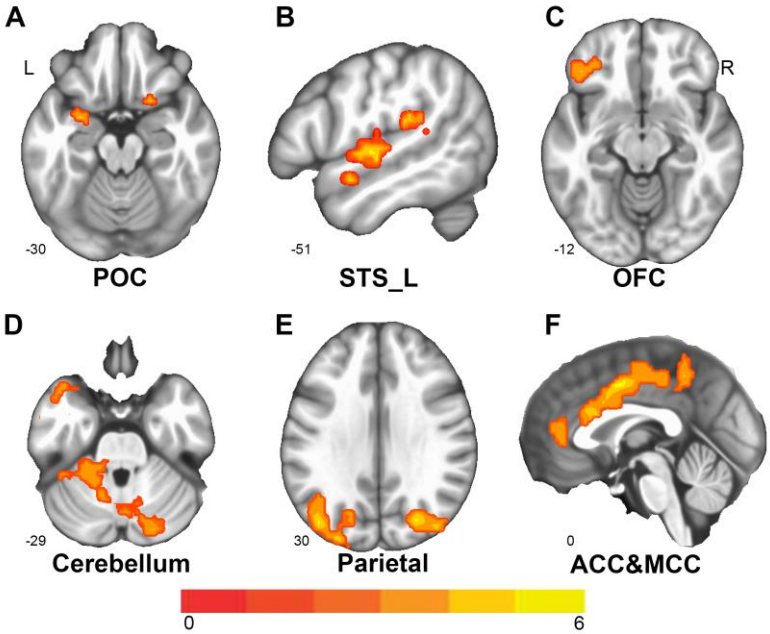

Figure 3. *Multisensory effects in the POC, left STS, orbitofrontal cortex (OFC), cerebellum, inferior parietal cortex (IPC), and the ACC (p<0.05, FDR corrected) during the weak air-puff experiment. Activity in the superior temporal gyrus (STG) was also detected. No such multisensory effects were observed for the strong air-puff experiment.*

3.3. Multisensory effects in the POC during olfactory-trigeminal interaction

We identified significant multisensory effects in the POC, suggesting that this structure may be involved in merging olfactory and trigeminal information. As shown in **Figure 4**, the mean beta (β) value, in the POC, during the PEA + weak air-puff condition satisfied the criterion that it be larger than the mean of its individual unisensory responses.

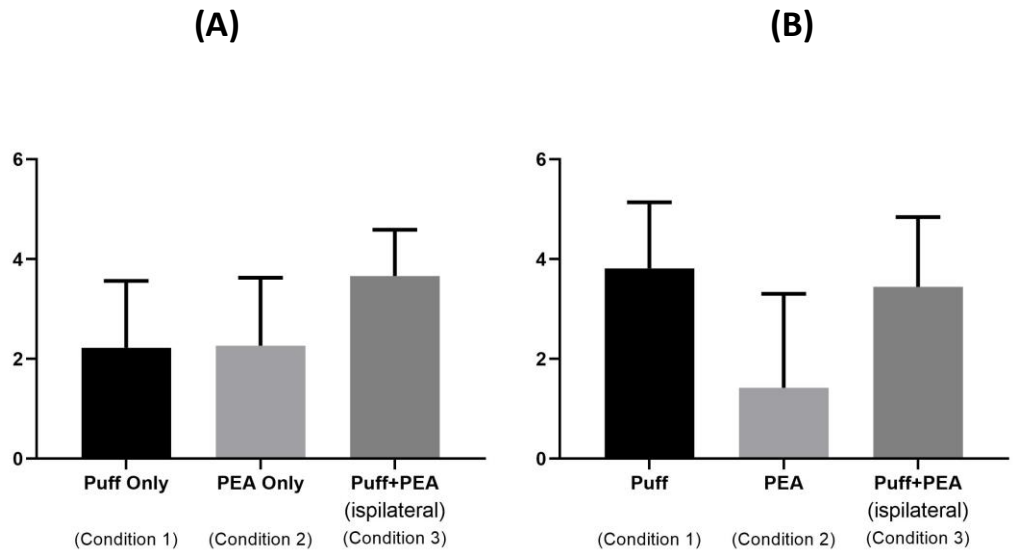

Figure 4. *POC response in terms of beta (β) values during Puff, PEA and Puff+PEA conditions.* ***(A)*** *Weak air-puff experiment showing multisensory effects, and* ***(B)*** *showing no multisensory effects in the strong air-puff experiment.*

We further analyzed the β value distribution within the activated POC volume. **Figure 5** shows that certain voxels satisfy the commonly used criterion for "super-additivity", i.e., multisensory responses are larger than the mean of their unisensory responses. Other voxels

within this volume satisfied the criterion that multisensory responses are larger than the maximum of their unisensory responses. Our data suggests that multisensory effects in the POC may be heterogeneous in nature, and that some voxels may exhibit significantly higher effects than others.

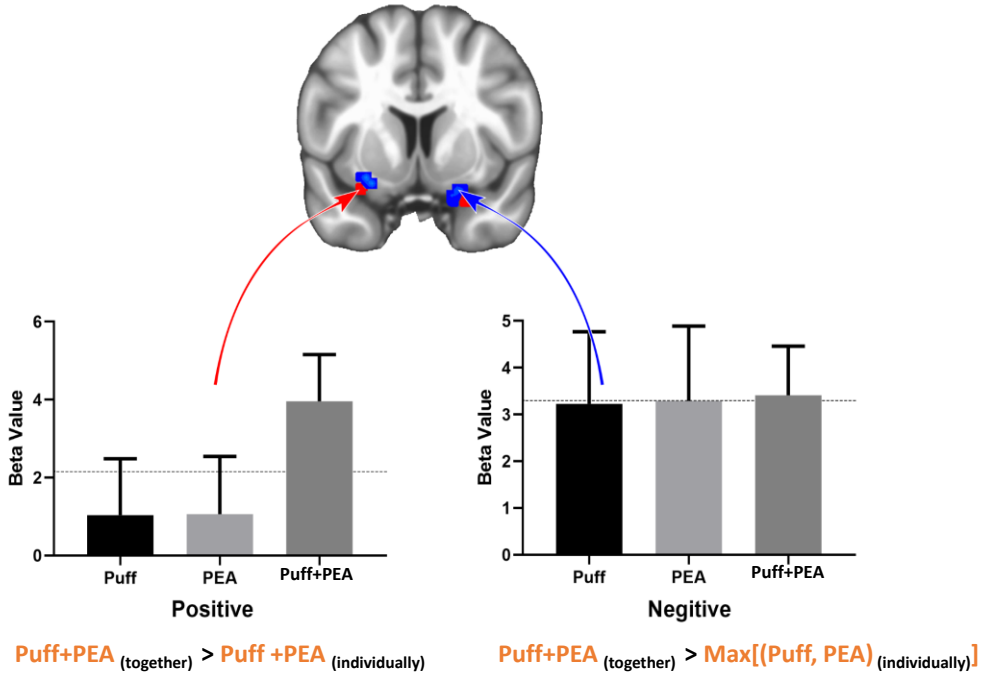

Figure 5. *Parameter estimates (beta [β]) within the POC during olfactory-trigeminal integration. POC activity compared to puff and PEA together, and individually (separately)* .

3.4. Multisensory effects in other brain regions during olfactory-trigeminal interaction

We also identified multisensory effects in the STG and IPC (**Figure 3**). The STS/STG is the auditory association cortex, and has been implicated in binding auditory–visual information. This region could serve a similar role in merging olfactory and trigeminal information [56]. The IPC's

role as a general filter and integrator of sensory information, within and across modalities, is well recognized. Subregions of the IPC [i.e., the inferior parietal lobule and intraparietal sulcus (IPS)] could potentially subserve attention for a specific modality over others [57]. For example, in visual, auditory and tactile modalities, the IPS appears to facilitate processes such as crossmodal localization and spatial attention [14, 58]. We suggest a similar role for the IPC during our localization experiments. As shown in **Figure 3**, we also observed multisensory effects during olfactory-trigeminal integration in the cerebellum. Previously, this structure has been implicated in olfactory processing. Following this hypothesis, observed cerebellar activity in this study may be related to a feedback mechanism linking and modulating intranasal somatosensory and odor information [59].

3.5. Multisensory effects mediating olfactory-trigeminal integration

While the present findings provide evidence for multisensory effects at the behavioral and neural levels, it remains unclear whether response enhancement in the POC and other areas actually predicted the extent of behavioral improvement. To address this issue, we performed correlation analyses by regressing the neural activation of subject-specific multisensory effects vs. changes in localization accuracy for weak-air puffs. There was a significant correlation between the magnitude of multisensory activity, and improvements in localization accuracy in the left POC. Similar significant correlations were observed in the STG, IPC, medial cingulate cortex (MCC), and the cerebellum (**Figure 6**). No such correlation was observed for orbitofrontal cortex (OFC) activity and localization accuracy. These findings support the idea that multisensory effects in the POC, STG, IPC, MCC, and cerebellum may underlie the observed behavioral enhancements during the weak air-puff localization experiment.

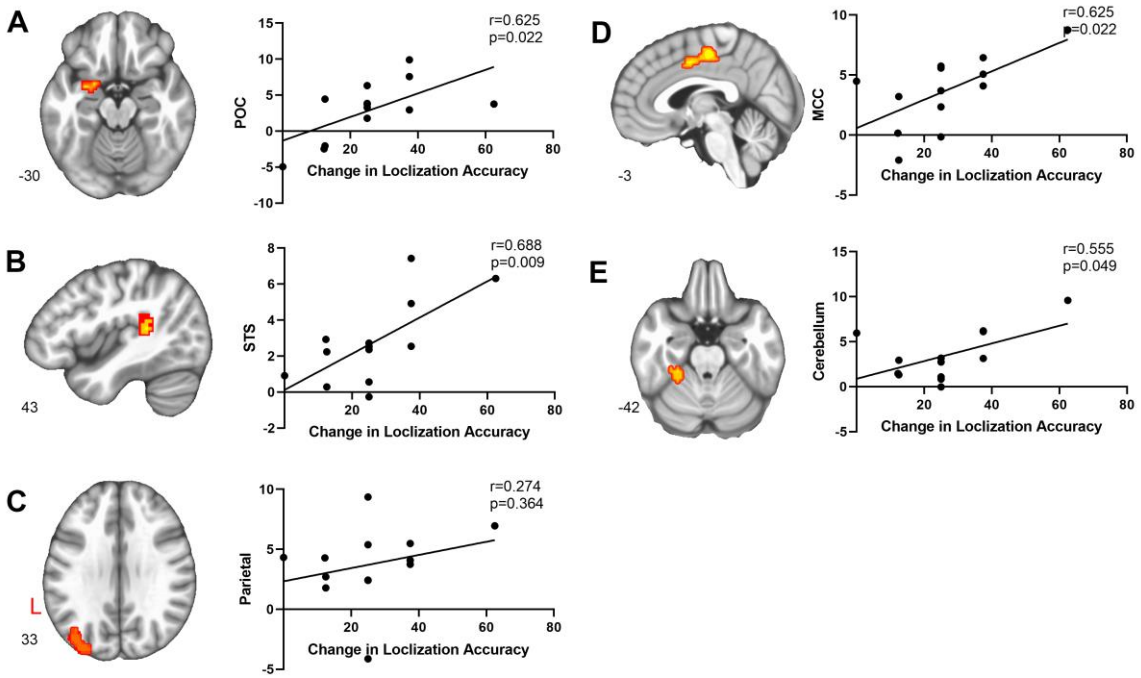

Figure 6. *Brain-behavior relationships. Scatterplots demonstrating strong correlations between multisensory fMRI activity and improvements in localization accuracy.*

3.6. Pathways mediating olfactory-trigeminal interaction

The stable multisensory effects in the OFC, i.e., not correlated with improvements in localization accuracy, suggests that integration between the olfactory and trigeminal systems do not induce profound modulations in OFC activity levels. Previously, Gottfried et al. (2003) identified a region of the OFC (adjacent to the POC) that is involved in merging olfactory and visual information. We; therefore, considered the possibility that changes in propagation of olfactory information, from the POC to the OFC, might account for the enhanced behavioral effects observed during the weak-air puff experiment. To test this possibility, we implemented an independent connectivity analysis using the generalized psychophysiological toolbox [49]. In this analysis, we tested brain regions that exhibited a general, multisensory-related modulation of connectivity with a seed region

(Methods). We then tested how these effects are related to changes in localization ability. Three seed regions (POC, STS and IPC) resulted in significant correlations, as shown in **Figure 7.** POC connectivity changed with both the OFC and cerebellum during olfactory-trigeminal integration. Similar connectivity patterns were observed in the STS and IPC, with the OFC and cerebellum (see **Figure 7**). Interestingly, the multisensory-specific increase in POC–OFC connectivity, and POC–cerebellar connectivity was directly related to changes in localization accuracy, as predicted by the significant positive correlation between multisensory-specific increases in connectivity and localization accuracy (**Figure 8**). However, STS connectivity to the OFC showed no significant correlation with respect to changes in localization accuracy. Its connectivity to the cerebellum showed a negative correlation, with changes in localization accuracy. These observations provide support for the hypothesized role of the cerebellum in olfaction: serving as a feedback mechanism that monitors and acquires sensory information for modulating sniffing behavior [59]. These findings suggest that functional couplings of the POC (along with other multisensory areas) are supporting odor-specific increases in activity, which enhances weak air-puff localization abilities.

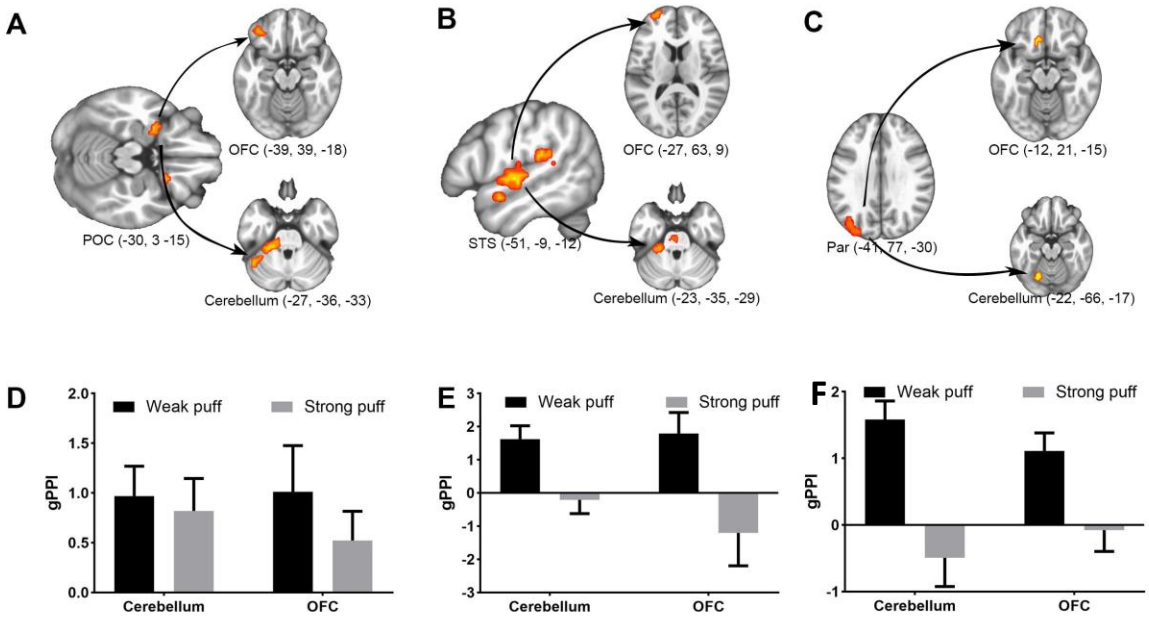

Figure 7. *Connectivity analyses with the POC, STS and IPC as seed regions. (**A**) POC seed regions were selected as clusters of activation from the multisensory effects analysis shown in **Figure 3** (thresholded at P < 0.05 corrected). Connectivity from the POC to the OFC, and from the POC to the cerebellum were enhanced during olfactory trigeminal integration (thresholded at P < 0.05 corrected). (**B**) STS/STG seed regions for the gPPI connectivity analysis were selected as clusters of activation from the multisensory effect analysis shown in **Figure 3** (thresholded at P < 0.05 corrected). Connectivity from the STS to the OFC, and from the STS to the cerebellum were enhanced during olfactory-trigeminal integration (thresholded at P < 0.05 corrected). (**C**) IPC seed regions were selected as clusters of activation from the multisensory effect analysis shown in **Figure 3** (thresholded at P < 0.05 corrected). Connectivity from the IPC to the OFC, and from the IPC to the cerebellum were enhanced during olfactory-trigeminal integration (thresholded at P < 0.05 corrected). (**D**) PPI parameters at the peak voxel in the POC-coupled cerebellum, and the POC-coupled OFC clusters corresponding to the Puff+PEA condition. (**E**) PPI parameters at the peak voxel in the STS-coupled cerebellum, and the STS-coupled OFC clusters corresponding to the Puff+PEA condition. (**F**) PPI parameters at the peak voxel in the IPC-coupled cerebellum and IPC-coupled OFC clusters corresponding to the Puff+PEA condition. Corresponding connectivity measures (D-F) from the strong puff experiment are shown for the purposes of comparison.*

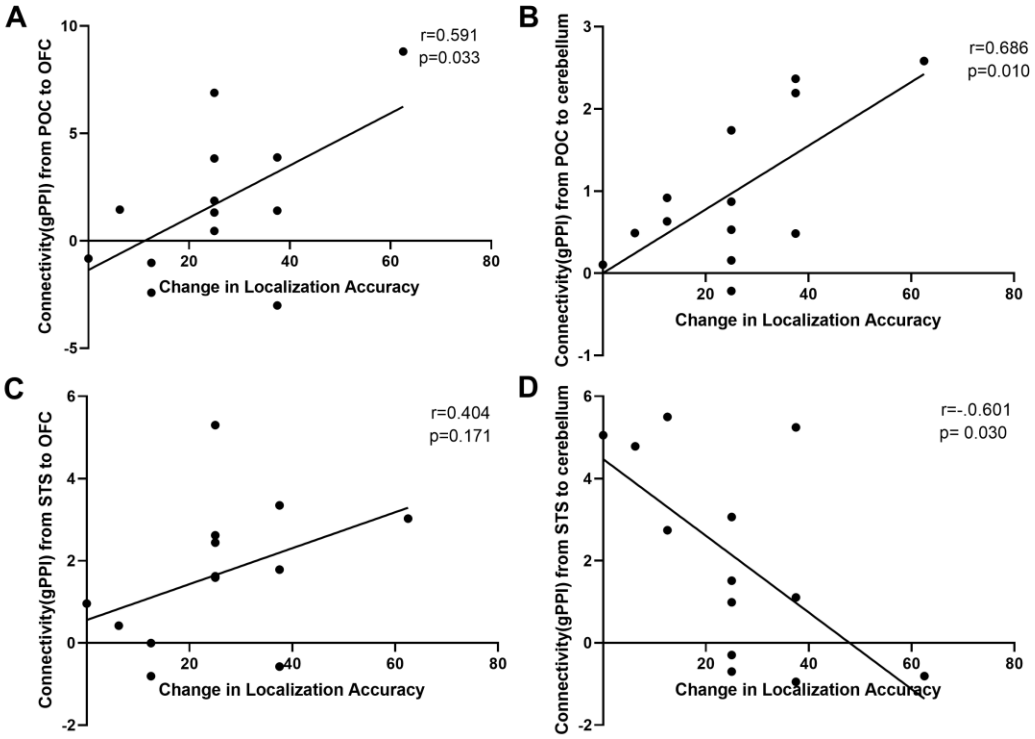

Figure 8. *Correlation between brain connectivity and behavioral changes. Connectivity between the* ***(A)*** *POC seed region and the OFC, and* ***(B)*** *the POC seed region and cerebellum were enhanced. Connectivity between* ***(C)*** *the STS seed region and the OFC showed no significant improvement during integration. In contrast, the connectivity between* ***(D)*** *the STS seed region and the cerebellum decreased during integration.*

4. DISCUSSION

The ability to merge different sensory information into coherent percepts is a fundamental ability of the central nervous system. This ability is important for the human olfactory system, which strongly relies on binding multimodal information to form olfactory percepts [60, 61]. Here, we addressed an unresolved question: How does the human brain integrate information from the olfactory and trigeminal systems? We found that this integration relies on enhanced fMRI activity in the POC, in addition to other known higher-order multisensory brain regions. Connectivity between these brain regions also seems to play a fundamental role in integrating information between the two systems. For example, connectivity between primary olfactory and other higher order multisensory areas were associated with enhanced performance during the localization task; thus, olfactory stimulation and the resulting differences in the perceived location of the air-puff stimuli crucially determine whether or not subsequent neural activity, and connectivity, are either enhanced or decreased. Taken together, our study suggests that a distributed brain network (including the primary olfactory cortex [POC]), may underlie sensory integration in the human chemosensory system. This study; therefore, extends our understanding of the neural substrates underlying multisensory integration, pushing it in a new direction.

The complex interplay between the olfactory and intranasal trigeminal systems endow humans with an innate ability to process information from overlapping neural circuitry within the nasal cavity [28]. Based on intensity evaluations, it has been proposed that this interaction may take place centrally [5]; although, there is support for peripheral interactivity as well—at the mucosal level [28]. This study focused on the primary olfactory cortex (POC) and therefore, dealt with the central aspects of olfactory-trigeminal interaction. The POC includes brain regions that receive direct inputs from the olfactory bulb, piriform cortex (PC), olfactory tubercle, entorhinal cortex, and amygdala [62, 63]. We hope that our findings will shed new light on the classical dogma, whereby olfactory and trigeminal information must reach known hierarchical

multisensory-specific brain regions *before* they can be integrated into logical and coherent perceptual experiences.

Research on multisensory integration in the olfactory system has mostly been conducted in rodents and, to a lesser extent, in humans. It has been shown that both gustatory [64] and auditory [20] stimuli can modulate single-unit activity in primary olfactory areas; taste stimulation has also been shown to induce responses in the rodent PC [65], and auditory tones have been known to induce responses in the rodent olfactory tubercle [20]. A human fMRI study by Gottfried et al.(2003) showed that visual facilitation of olfactory detection enhanced activity in the OFC which is distinct from, but interconnected with, the POC [66]. Using phase synchrony, Zhou et al. (2019) showed that primary olfactory cortical areas support multisensory integration within the olfactory system [67]. Additionally, simultaneous presentation of pure trigeminal and pure olfactory stimuli led to higher cortical activation in the OFC and insula (INS), although this study did not demonstrate the integration of olfactory and trigeminal stimuli in the POC [68]. The olfactory bulb (OB) is known to subserve olfactory-trigeminal integration [25, 69-71], however its structure cannot be easily imaged with fMRI at 3T; therefore, we did not focus on the OB in this study, despite its relevance to olfactory–trigeminal integration.

Our localization experiments followed the three fundamental principles of multisensory integration: the spatial rule, the temporal rule, and the principle of inverse effectiveness [38]. Our data showed that presenting PEA and the weak air-puff in the same nostril (i.e., spatial coincidence) facilitated integration. This rule states: when space is relevant to a task, multisensory integration is enhanced for stimuli in different sensory modalities if they are being presented from the same spatial location. Our experiment also agrees with the temporal rule (though we did not test it formally). Maximal integration was observed when PEA and weak air-puffs were presented simultaneously. Finally, our experiment followed the principle of inverse effectiveness, which states that multisensory integration is more effective when stimuli are weaker than when they are strong [72].

The same trigeminal nerve (Cranial nerve V) conveys both chemosensory and somatosensory intranasal trigeminal stimuli, but they appear to be relatively independent, behaviorally [33]. The quality aspect of odors is independently conveyed via the olfactory nerve (Cranial nerve I) which is modulated, i.e., usually reduced, in the presence of trigeminal co-stimulation [3, 4]. The trigeminal system has been extensively investigated using odor localization tasks which aim to stimulate the trigeminal nerve [26]. Unlike many behavioral experiments demonstrating response enhancement, our forced-choice localization task, with PEA, provided an important control for attentional focus, thereby demonstrating an effect of sensory integration based on the grounds of absolute localization, and not merely on attentional capture. Our results provide compelling evidence for the functional significance of neural responses to combinations of odor and intranasal somatosensory stimuli, as well as the existence of a potential "central locus" where neural inputs (conveying olfactory and trigeminal information) are integrated: an 'olfactory' substrate. Our data suggests that the POC, when presented with one element of a stimulus pair, can reduce the detection threshold for other sensory stimuli. The impetus for testing such a hypothesis using fMRI was provided by our behavioral study [73] . Furthermore, a behavioral effect similar to what we have observed has been reported between the olfactory and chemosensory trigeminal stimuli [26]. Future studies should seek to clarify the underlying neural mechanisms of this integration: given that stronger interdependencies have been hypothesized between the olfactory and chemosensory trigeminal systems.

Passive stimulation by air puffs closely mimics airflow changes inside the nasal cavity due to sniffing [37]. Sniffing is an active process of stimulus transport, and is considered to be an integral and necessary part of the olfactory percept. For example, odor intensity and identity percepts are modulated by patterns of sniffing [36]. It has been shown that activity in the POC is driven by the somatosensory component of sniffing, i.e., the airflow changes in nostrils. The main contribution of our study shows that the perception of the somatosensory component of sniffing behavior can be modulated by olfactory information. Furthermore, we provide convincing fMRI

evidence suggesting that the POC is a potential site for this dynamic multisensory interaction. It is abundantly clear that multisensory representations in the POC directly inform the decision making process during our localization task. This agrees with crossmodal facilitation of identity between vision and audition [74] or audition and somatosensation [75], where enhanced activation has been observed in sensory-specific cortical areas.

The POC has reciprocal connections with the OFC, a structure that showed multisensory effects during our olfactory-trigeminal integration experiment [76, 77]. Although OFC activity was not modulated by task performance, our findings remain consistent with previous research. Visual facilitation of olfactory detection has been shown to enhance activity in the heteromodal OFC regions [22]. The OFC is also a critical site for flavor processing because of its sensitivity to olfactory, gustatory, visual, and mouth feel sensory inputs [78]. Corroborating a study by Kareken et al (2004), our data suggests that enhanced, but consistent, OFC activity may be related to olfactory exploration, or more generally, expectancy [79]. Our study suggested that the POC is a crucial site for olfactory-related associative processing. We then reasoned that multisensory effects in the OFC might instead be explained by its connectivity with the POC. Indeed, our results supported this hypothesis because the altered connectivity between the POC and OFC was correlated with odor and nostril specific increases in the localization accuracy of weak air-puff stimuli.

Additional activations, dependent on task performance, were seen in multisensory areas such as the STS/STG and the inferior posterior cortex (IPC). The STS is known to subserve the crossmodal binding of features in auditory and visual modalities. The enhanced STS activation in our study may be related to the crossmodal integration of features between olfactory and trigeminal stimuli, rather than the task of localizing the stimulated nostril. On the other hand, the heteromodal IPC is known to mediate the crossmodal localization of objects in space, which may be more relevant to the weak air-puff localization task. This view of the IPC is consistent with the general role for its involvement in spatial and temporal attention [58]. Although attention and

crossmodal binding have been shown to represent two distinct brain processes [80], our data shows that response patterns in the STS and IPC are also relevant to chemosensation, and that these brain regions (long classified in non-olfactory terms) may in fact be involved in a far wider spectrum of sensory information. Our findings imply that the POC, STS, IPC, cerebellum, and MCC are all contributing factors for the formation of the multisensory olfactory percept. Future studies should clarify the functional contributions of these brain structures.

Although activity in the cerebellum during olfactory stimulation has previously been reported, its role in the chemical senses still remains unclear [59, 81]. Studies in individuals with olfactory deficits have also highlighted a role for the cerebellum in olfaction (e.g., Bitter et al. 2010a, 2010b; Peng et al. 2013). These findings have led to the premise that (e.g., Bensafi et al. 2008; Iannilli et al. 2011) this structure is part of a complex integrative system (comprising the cerebellum, the entorhinal cortex, sensory areas, and frontal regions), which is related to the intensity coding of olfactory stimuli [82, 83]. Likewise, Small et al. (2003) reported intensity dependent cerebellum activity (irrespective of valence) during gustatory stimulation, and suggested a role for the cerebellum in processing stimulus intensity during chemosensation. Previous research also suggests a role for the cerebellum in multisensory integration [14, 84-86]. Non-human primate data has also suggested that different sensory areas of the cerebral cortex converge upon common areas within the neocerebellum [87-89]. In our study, the activity and connectivity of the cerebellum displayed multisensory effects, and predicted behavioral improvements in the localization tasks. The hypothesized involvement of the cerebellum in a feedback mechanism (during olfactory processing) is supported by our data. This study provides crucial information in testing a functional hypothesis regarding the cerebellum. Specifically, its involvement in olfactory-trigeminal integration.

Subjects with olfactory deficits often exhibit decreased chemosensory trigeminal sensitivity. Because olfactory information can influence the perception of air-puff stimuli, we hypothesize that somatosensory trigeminal sensitivity may be affected in anosmic subjects [90]—

challenging the notion that chemosensory and somatosensory systems are relatively independent. Our results, and those of Tremblay et al. (2019), supports a general mechanism by which the olfactory system interacts with the intranasal trigeminal system. The POC is a potential brain structure for integration, regardless of whether the olfactory information is merged with chemosensory or somatosensory trigeminal information. As a result, we predict that multisensory effects in the POC might be reduced for both chemosensory and somatosensory stimulation in anosmic subjects. Such findings will strengthen and support the hypothesis that trigeminal system responses are independent of trigeminal receptors, or the type of stimulation [91]. If so, then measuring the sensitivity of one trigeminal stimulus may suffice as a general assessment of the trigeminal system as a whole [34].

Apart from our main objective: determining the multisensory integrative circuitry for olfactory and trigeminal systems, our study provides a basis by which several critical barriers to progress in the field may be addressed. (1) Aging affects the interdependencies of the olfactory and intranasal trigeminal systems; understanding deficits in integration may be a crucial first step in delineating the aging effects for both systems [92]. (2) Olfactory deficits are also preclinical symptoms in Alzheimer's disease (AD) and Parkinson's disease (PD) [93-96]. The mechanisms of multisensory integration (between olfactory and trigeminal systems) might be differentially affected in AD and PD. Such information will be of great clinical and research interests, as it would be critical in developing sensitive biomarkers capable of identifying and monitoring people at risk for developing AD and/or PD.

The current results identified a distributed activity pattern across a multisensory network that may collectively support olfactory and trigeminal perception. Our data highlights the importance of multisensory effects in the primary olfactory cortex (POC), when integrating olfactory and intranasal somatosensory stimuli. Such early sensory integration allows the brain to make decisions based on multisensory information, rather than relying on any single unisensory input. These results coincide with hypotheses related to audio–visual–somatosensory

integration. Our findings show that olfactory-trigeminal integration is also supported by brain regions outside the POC. This integration seems to suggest that (as is the case with vision, audition, gustation and olfaction) spatial coincidence is a key factor determining whether integration is taking place. The results described herein indicate that the basic principles of crossmodal integration are preserved across brain structures and modalities.

5. REFERENCES

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