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Tractography indicates lateralized differences between trigeminal and olfactory pathways

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ABSTRACT

Odorous sensations are based on trigeminal and olfactory perceptions. Both trigeminal and olfactory stimuli generate overlapping as well as distinctive activations in the olfactory cortex including the piriform cortex. Orbitofrontal cortex (OFC), an integrative center for all senses, is directly activated in the presence of olfactory stimulations. In contrast, the thalamus, a very important midbrain structure, is not directly activated in the presence of odors, but rather acts as a relay for portions of olfactory information between primary olfactory cortex and higher-order processing centers. The aims of the study were (1) to examine the number of streamlines between the piriform cortex and the OFC and also between the piriform cortex and the thalamus and (2) to explore potential correlations between these streamlines and trigeminal and olfactory chemosensory perceptions. Thirty-eight healthy subjects were recruited for the study and underwent diffusion MRI using a 3T MRI scanner with 67 diffusion directions. ROIs were adapted from two studies looking into olfaction in terms of functional and structural properties of the olfactory system. The "waytotal number" was used which corresponds to number of streamlines between two regions of interests. We found the number of streamlines between the piriform cortex and the thalamus to be higher in the left hemisphere, whereas the number of streamlines between the piriform cortex and the OFC were higher in the right hemisphere. We also found streamlines between the piriform cortex and the thalamus to be positively correlated with the intensity of irritating (trigeminal) odors. On the other hand, streamlines between the piriform cortex and the OFC were correlated with the threshold scores for these trigeminal odors. This is the first studying the correlations between streamlines and olfactory scores using tractography. Results suggest that different chemosensory stimuli are processed through different networks in the chemosensory system involving the thalamus.

1. Introduction

The sense of smell is one of the many senses that makes us aware of our environment. Functionally, this sense is bimodal with the trigeminal and olfactory systems working together in concert (Cain, 1974; Hummel and Livermore, 2002). Olfactory stimulants predominantly activate the piriform cortex, insular cortex, amygdala whereas chemosensory trigeminal stimuli, in addition to these areas, also activate the thalamus and substantia nigra (Joshi et al., 2021; Albrecht et al., 2010). The olfactory system is related to complex brain functions like emotions or memory (Soudry et al., 2011).

These brain functions are mediated by white matter connections between the many "olfactory areas" and higher cognitive processing centers. Such white matter fiber streamlines can be visualized using diffusion MRI (DMRI). Fiber tractography, which is derived from DMRI, is an *in-vivo* approach to visualize white matter fibers and has been used in various contexts, e.g., central and peripheral nervous system visualization, or whole brain white matter reconstruction (Basser et al., 2000; Sarwar et al., 2019). DMRI has also been used to better understand the olfactory system. One of the first studies presented the olfactory tract (OT) *in-vivo* using diffusion tensor fiber tractography (Skorpil et al., 2011). The authors visualized in five healthy controls a small white matter tract originating from the olfactory bulb, connecting to inferior surfaces of the frontal lobe. No such streamlines could be found in a patient with congenital anosmia which was seen as validation of the methodology. More recently, using a constrained spherical deconvolution (CSD) diffusion model Milardi et al. (2017) could visualize the OT directly projecting to the piriform cortex, the entorhinal cortex and the amygdala and furthermore to the orbitofrontal cortex.

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Fiber tracking within the olfactory system is complicated as the system is intimately connected with other brain regions, e.g., thalamus, cerebellum, and insula (Soudry et al., 2011). Another complication is that some regions that are directly involved in olfaction, such as piriform cortex or the entorhinal cortex, are structurally difficult to delineate. The piriform cortex, part of the olfactory cortex, has many projections to other brain regions such as the amygdala and hippocampus, playing a major role in converting sensory input into specific behavioral output (Chen et al., 2014; Diodato et al., 2016). On the other hand, the orbitofrontal cortex (OFC), a secondary olfactory area, is not solely dedicated to olfactory processing but is, for example, strongly involved in sensory integration (Wang et al., 2020). Whilst there is a consensus about olfactive information processing between the piriform cortex and OFC, there is less agreement about the role of the thalamus. Some authors (Shepherd, 2005) consider that the exact role of the thalamus in olfaction is not clear and that there seems to be no direct involvement of the thalamus in the connections between the piriform cortex and the OFC. In contrast, Courtiol and Wilson concluded that the thalamus serves as a crucial center for olfactory processing by forming a reciprocal connection with the OFC via the piriform cortex (Courtiol and Wilson, 2015).

In order to assess the role of the connections between the piriform cortex, thalamus and OFC, we aimed to examine white matter streamlines within the olfactory system using fiber tractography. Additionally, we explored how the processing of olfactory versus trigeminal odors (Joshi et al., 2021) impacted potential relations between these streamlines.

2. Methods

2.1. Participants

Thirty-eight healthy subjects (20 males, 18 females) were recruited to take part in the study after having provided written informed consent. The experiments were conducted according to the Helsinki declaration. The ethics committee at the medical faculty of the Technical University of Dresden approved the study design (approval number EK558122019). A detailed, structured medical history (Hummel and Welge-Lüssen, 2006) was conducted including questions regarding drinking habits, smoking, medications, or current disorders. The sample size is always debatable in functional or structural studies. Still, considering previous work (Joshi et al., 2021) a sample above 30 is thought to provide reliable results.

2.2. Olfactory testing

A normal sense of smell was ascertained using the “Sniffin’ Sticks” odor identification test with maximum score of 16. This test is based on a forced choice paradigm where subjects have to identify 16 odors at suprathreshold concentrations using flash cards with four verbal descriptors each (Oleszkiewicz et al., 2019). For olfactory activation in the MR scanner, we used four odors (provided by Takasago, Paris, France), two more trigeminally active stimuli and two more olfactory active stimuli. The trigeminal odors were peppermint (order number ABX321352) and spearmint (ABX321351A), the olfactory stimuli were cherry (ABX321603) and strawberry (ABX321354A). Prior to the administration in the MR environment each of the pure, undiluted odors was rated by the participants for their intensity and pleasantness using visual analogue scales (0–10, with 0 meaning no intensity perceived / extremely unpleasant and 10 meaning extremely intense / extremely pleasant). Threshold scores (1 to 8, with 1 meaning high threshold [relatively insensitive] and 8 meaning low threshold [very sensitive]) for each odor were also obtained from each participant using a 3-alternative forced choice task with odors presented in glass bottles using a staircase design (Hummel et al., 1997) (4 ml odor in 50 ml volume bottles with an opening of 4 cm diameter). Participants had to discriminate the odor-containing bottle from two others containing the solvent propylene glycol (Sigma-Aldrich, Deisenhofen, Germany, order number 398039). All tests were performed within a forced choice design.

The two trigeminal odors (peppermint and spearmint) did not differ statistically (t-test) in terms of threshold ($p = 0.83$), or intensity ($p = 0.45$) but differed in terms of pleasantness ($p = 0.02$). Still, peppermint and spearmint were categorized and combined together as “trigeminal odors” activating both the olfactory and trigeminal systems (Han et al., 2020; Krone et al., 2001; Joshi et al., 2021). Their trigeminal nature was characterized by lateralization tests where 20 randomized odor pairs (in two squeeze bottles) are presented to each nostrils where one bottle contained no odor whereas the other did contain an odor (Frasnelli et al., 2011). The two olfactory odors did not differ in intensity ($p = 0.09$), pleasantness ($p = 0.93$) and threshold ($p = 0.53$) and were categorized and combined together as “olfactory odors” with little or no activation of the trigeminal system (Pellegrino et al., 2017).

2.3. Image acquisition

All image data was acquired on a 3T Prisma (Siemens Healthcare, Erlangen, Germany) MRI scanner, using a 32-channel head coil. A 3D magnetization prepared gradient echo T1 image was acquired (TR = 2000 ms, TE = 1.95 s, FoV = 256 mm × 256 mm, slice thickness = 1.7 mm and voxel size of 1 × 1 × 1 mm). A diffusion weighted, generalized auto-calibrating partial parallel acquisition (GRAPPA) sequence image (TR = 6070 ms, TE = 100.8 ms, multiband acceleration factor = 2, 67 diffusion directions, b-value = 1000 s/mm^2, slice thickness = 1.7 mm, voxel size = 1.7 × 1.7 × 1.7 mm) was acquired. b0 images, no diffusion images, were also acquired in 6 directions which resulted in longer TR = 12,110 ms and did not affect tensor fitting.

2.4. Image analysis

All image analysis was carried out in FSL, a FMRIB software from the Oxford center for functional magnetic resonance imaging of the brain version 6.0.2(Jenkinson et al., 2012) more specifically, FDT (FSL diffusion toolbox) was used. A standard pipeline was used for pre-processing of the diffusion data which included head motion, eddy current correction using eddy from FDT, and followed by removal of non-brain tissue using bet. Using Quality assessment of diffusion (QUAD) we assessed quality at subject level and Study-wise quality assessment of diffusion (SQUAD) for group level, where a cut-off value for mean displacement was set at > 2 mm in terms of absolute motion and > 0.3 mm in terms of relative motion for the whole study population (Bastiani et al., 2019). No dataset had to be discarded. BedpostX was used to map out diffusion parameters at each voxel (Behrens et al., 2007).

2.5. Fiber tracking

Tractography was performed using PROBTRACKX probabilistic tracking in FDT diffusion toolbox (Behrens et al., 2007). For seed space, a single mask option was chosen with piriform cortex as the mask. Further, since the mask was not defined in diffusion space, appropriate transforms (from structural space to diffusion space) were selected as tracking is performed in diffusion space. In optional targets, waypoint mask, exclusion mask and termination mask were chosen, where the midline mask was selected as an exclusion mask (Lancaster et al., 2000). By keeping the waypoint and termination mask as the same, we make sure that all streamlines that (1) start from the piriform cortex pass through the orbitofrontal cortex and also end there or all streamlines that (2) start from piriform cortex pass through the thalamus and also end there will be counted.

ROIs were used from already published data (Fjaeldstad et al., 2017; Seubert et al., 2013). They were mapped to each subject in two steps; since the ROIs were defined in structural space or rather MNI space,

Table 1
Psychophysical data. Intensity and pleasantness ratings ranged from 0 to 20 because here the scores for olfactory and trigeminal odors were combined as mentioned in method section. Threshold scores ranged between 1 and 16. All values are presented as mean ± SD, for olfactory and trigeminal odors.

Age: 26.1 ± 3.0 years, 20 male, 18 female	Olfactory odors (Strawberry and cherry)	Trigeminal odors (Spearmint and peppermint)
Intensity (0–20)	15.0 ± 3.0	13.1 ± 3.5
Pleasantness (0–20)	10.5 ± 4.5	12.8 ± 3.1
Threshold (1–16)	12.9 ± 1.4	13.6 ± 1.6

firstly FLIRT (Jenkinson and Smith, 2001) was used to obtain a linear transformation matrix between diffusion and structural space and then FNIRT (Simpson et al., 2015) was used to obtain non-linear transformation to store results in standard space. ROIs from Seubert et al. were derived using ALE from 40 different functional olfactory studies. These authors also mentioned that they initially had insular cortex included in the mask; it was removed in order to increase functional homogeneity of the OFC and piriform cortex mask. ROIs from Fjaeldstad et al. were superimposed. The ROIs from Fjaeldstad have been derived using functional and structural connectivity patterns from 16 healthy participants and include others olfactory related regions as well. Superimposing here means to overlay masks from Seubert et al. over the mask from Fjaeldstad et al., considering the latter as standard and keeping the congruent areas. We used this approach for reducing false positives in tracking which might have occurred if we had used a larger mask instead. Each mask was then reviewed by an expert neuroradiologist (CG). The mask for the OFC included only the central part. Thalamus, as a mask, was chosen from Harvard-Oxford subcortical structural atlas (Frazier et al., 2005). This atlas does not divide the thalamus based on its nuclei because this atlas is largely taken from functional studies. We also thresholded the mask. All ROIs were thresholded using fslmaths (Lancaster et al., 2000). For the purpose of calculating the streamlines between ROIs, the waytotal number was used. The waytotal number was derived as one of the metrics while running probtrackX, and it infers the total number of streamlines for all seed voxels (piriform cortex) which have not been rejected. The volume of the tract was not computed. Simple tracking was performed from piriform cortex to orbitofrontal cortex or Thalamus and the waytotal number was used to determine how many streamlines made it to the termination mask.

2.6. Statistics

We used non-parametric Kruskal-Wallis ANOVA independent samples test with Mann-Whitney U test for pairwise comparisons using Bonferroni corrections. We ran the test for side (left and right) and track pathway. We also ran partial correlations between track pathways and identification scores, threshold scores, intensity, and pleasantness ratings. A p-value < 0.05 was considered to be significant. All statistical analysis was performed using SPSS v27.0 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Psychophysical data

The mean age for the whole population was 26.1 ± 3.0 years (Table 1). Participants had an average identification score of 13.6 ± 1.4 (mean ±SD) indicating normal olfactory function. Psychophysical data including intensity, pleasantness and threshold scores are summarized in Table 1. No gender-related differences were found.

3.2. Tracking

3.2.1. Comparison between streamlines piriform-OFC vs. piriform-thalamus

In the left hemisphere streamlines between piriform cortex and thalamus were significantly more in comparison to streamlines between piriform cortex and OFC (X^2 (df 1) = 8.52, $p = 0.004$). However, in the right hemisphere, streamlines between piriform cortex and OFC were more in comparison to streamlines between piriform cortex and thalamus (X^2 (df 1) = 6.5, $p = 0.01$) (Fig. 1).

3.2.2. Comparison between hemispheres

Lateralized differences reveal that streamlines were higher between piriform cortex and OFC in the right hemisphere (X^2 (df 1) = 11.8, $p = 0.001$). However, no lateralized differences in streamlines between piriform cortex and thalamus could be found (X^2(df 1) = 3.5, $p = 0.06$) The graphical representation of the outputs from the tractography analysis are summarized in Figure 2.

3.3. Correlations between results from tractography and stimulus intensity/thresholds

A partial correlation analysis, controlling for age, revealed that streamlines between both left and right piriform cortex to thalamus exhibited positive correlations with intensity ratings for trigeminal odors ($r = 0.40$, $p = 0.01$, and $r = 0.33$, $p = 0.03$ respectively). A positive correlation between the number of streamlines (piriform cortex to OFC) and threshold score for trigeminal odors ($r = 0.40$, $p = 0.01$) were also seen. However, no such correlation was seen for olfactory odors with any of the streamlines (Fig. 3 and Table 2).

4. Discussion

Using probabilistic tractography *in vivo*, the probability map of the olfactory system in humans was illustrated where white matter streamlines could be visualized from the piriform cortex to the OFC and also from the piriform cortex to the thalamus. The main findings were (1) a significantly higher number of streamlines between the piriform cortex and the thalamus in the left hemisphere and (2) a higher number of streamlines between the piriform cortex and the OFC in the right hemisphere. Moreover, (3) the streamlines between the piriform cortex and the OFC were more prominent in the right hemisphere. Last, but not least, (4) we found that the number of streamlines between the piriform cortex and the thalamus positively correlated with the perceived intensity and streamlines between the piriform cortex and the OFC with threshold of trigeminal odors.

The present tractography analysis showed the presence of significantly higher streamlines in the right hemisphere. This is in line with previous research (Zatorre et al., 1992; Royet et al., 2001) where authors noted higher neural activity in the right OFC in response to passive odor stimulation. Positron emission tomography based studies (Royet et al., 2001, 1999) found that odor judgements based on familiarity activate the right OFC, whereas hedonic judgements activate the left OFC. In contrast, a study based on the above mentioned assumptions showed that odor familiarity specifically invokes piriform cortex and brain areas like, entorhinal cortex, amygdala, inferior gyrus, possibly through a thalamic relay, among other possibilities (Plailly et al., 2005).

The role of the thalamus is debated when it comes to olfaction. The mediodorsal thalamic nuclei (MDT) act as an important relay in olfaction, and that piriform cortex has been shown to have excitatory projections to MDT nuclei in rats (Courtiol and Wilson, 2015; Cornwall and Phillipson, 1988). A comprehensive review of the literature suggests that

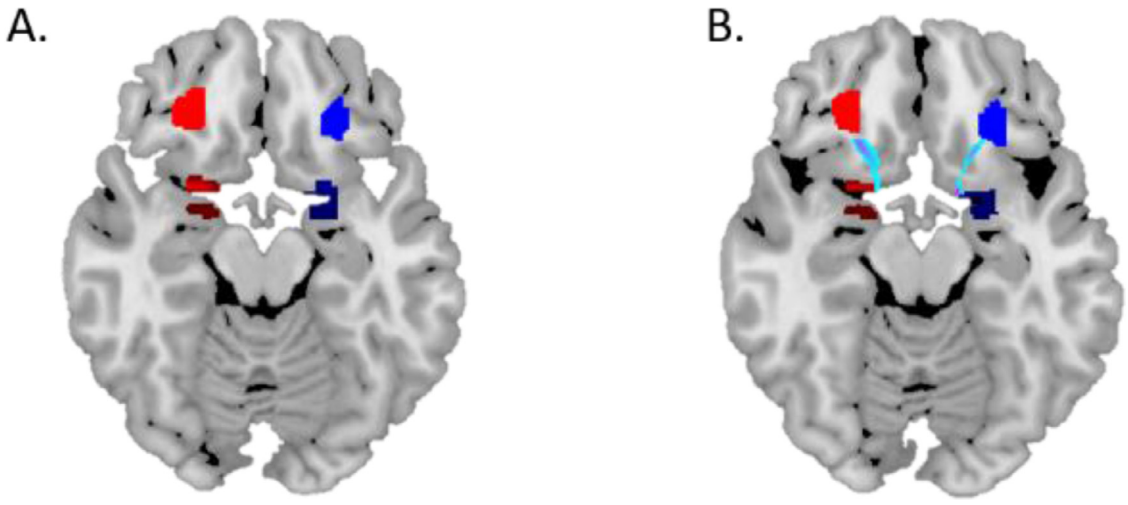

Fig. 1. Represents the ROIs for olfactory cortex and the tractography outputs. A represents the olfactory cortex masks, namely left piriform cortex and OFC (blue) and right piriform cortex and OFC (red). B represents streamlines (light-blue) between piriform cortex and OFC using probabilistic tractography. ROIs; region of interests, OFC; orbitofrontal cortex.

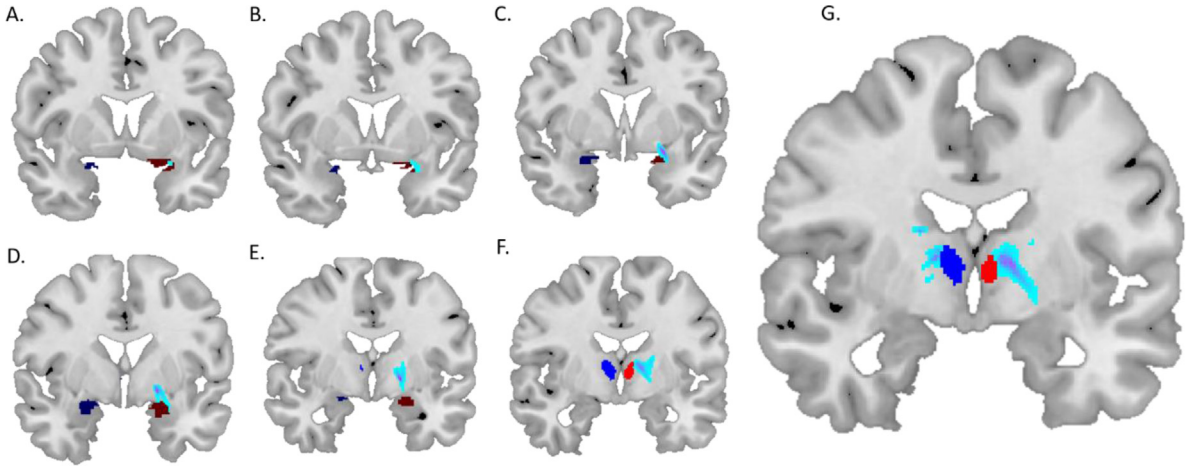

Fig. 2. Represents the track convergence from piriform cortex to thalamus represented from A to F.G represents bilateral streamlines (light-blue) between piriform cortex and thalamus using probabilistic tractography. Left thalamus is represented by red color and right thalamus by blue color.

Table 2
Tractography results in terms of number of streamlines. Brain hemisphere represents which side tracking was performed and tracking direction represents the ROIs used as initiation and termination masks.

Side (Brain hemisphere)	Tracking direction	Number of tracts (Mean ± SD)	p-value (for significance p<0.05)
Left	Piriform cortex OFC	1389 ± 2807.7	0.004
	Piriform cortex — Thalamus	4215 ± 6379.6	0.001
Right	Piriform cortex — OFC	7356 ± 11421.8	0.01
	Piriform cortex Thalamus	2420 ± 5188.4	

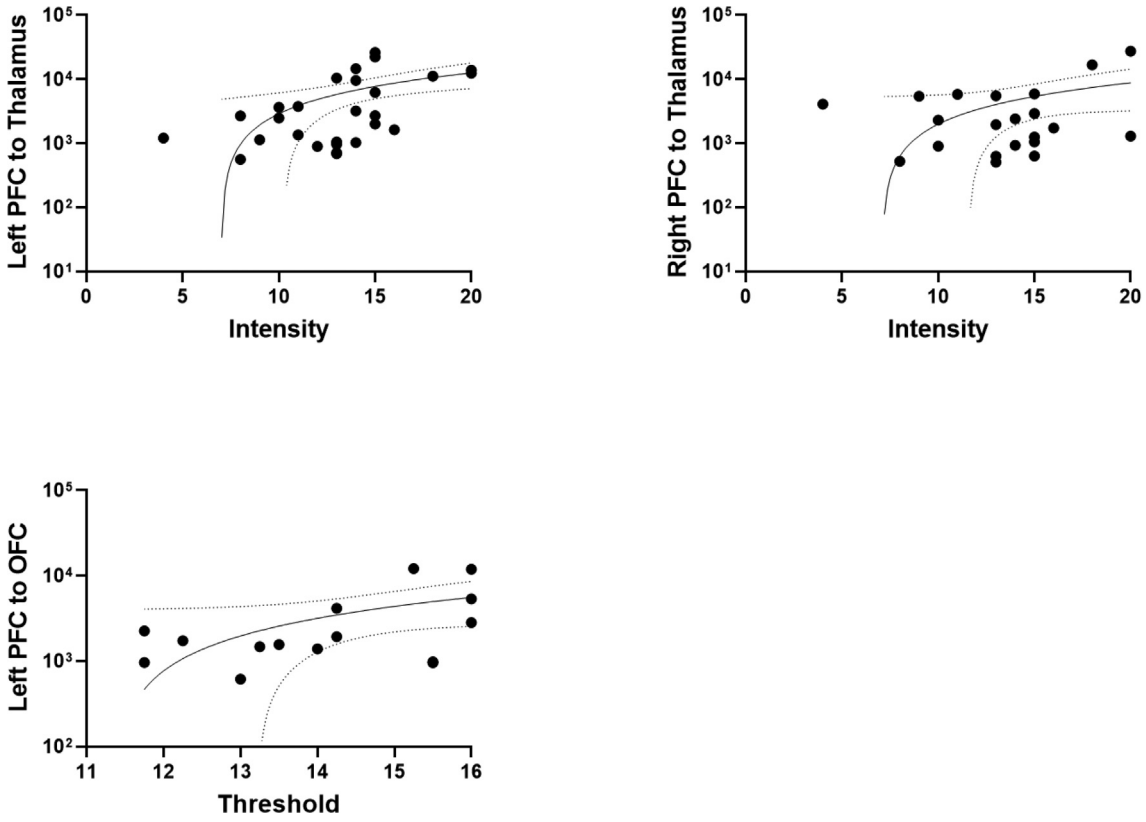

Fig. 3. Partial correlation analysis. The top row represents positive correlations between intensity score for trigeminal odors and left and right streamlines between PFC and Thalamus, respectively. The bottom row represents positive correlations between threshold scores for trigeminal odors and left streamlines between PFC and OFC path. PFC, piriform cortex, OFC, orbitofrontal cortex.

the orbitofrontal cortex has close relations with the thalamus. However, when it comes to connections between the piriform cortex and the thalamus, not much is known (Soudry et al., 2011). It may be that the thalamus functions as a relay center providing a link between olfactory processing streams from various brain areas, similar to the amygdala, the nucleus accumbens, the anterior cingulate or the somatosensory system (Courtiol and Wilson, 2015) or as in rats, that there is a direct connection between the piriform cortex and the thalamus. Hence, for example valence of odor may be partly generated through these multi-synaptic connections between the thalamus and olfactory eloquent structures like the piriform cortex. However, in the present study we did not find any such correlations for olfactory odors (cherry & strawberry). In contrast, trigeminal odors (peppermint & spearmint) being somatosensory stimuli have been shown to produce robust activations in the thalamus (Frasnelli et al., 2011; Hummel and Frasnelli, 2019; Pellegrino et al., 2017). This duality of the stimulation may also explain the observed correlation between streamlines between the piriform cortex and the thalamus and intensity ratings for trigeminal odors but not for olfactory odors.

Correlation analysis revealed that the trigeminal odor threshold scores had positive correlations with the streamlines between piriform cortex and OFC whereas intensity scores for trigeminal odors had positive correlations with streamlines between the piriform cortex and the thalamus. Odor threshold scores are based on a simple 3-alternative forced choice olfactory task which does not involve major cognitive functions. This is consistent with previous studies where authors found performance in threshold tests to be unrelated to cognitive factors (Hedner et al., 2010). This is also in accordance with the previous literature which suggests strong involvement of the OFC in odor perception (Zald et al., 2002). Olfactory tasks with higher cognitive load like intensity ratings, verbal identification tasks, or pleasantness ratings activate secondary olfactory areas, like amygdala, hippocampus, anterior cingulate cortex and thalamus (Soudry et al., 2011). In the present study intensity scores were found to be positively correlated to streamlines between the piriform cortex and the thalamus possibly indicating that the processing of this information requires a higher degree of networking. The bimodal nature of the “trigeminal odors” may lead to a higher degree of memorization, because of their activation of two sensory system (Joshi et al., 2021; Pellegrino et al., 2017; Livermore et al., 1992). A practical consequence of that may be, for example, the high identification rates typically found for the bimodal trigeminal/olfactory peppermint in odor identification tests compared to the lower rates of identification typically found for the less trigeminally active stimuli cinnamon or pineapple (Hummel et al., 1997; Doty et al., 1984). Probabilistic tractography can be hampered by false-positives (Sarwar et al., 2019). A recent review pointed out that tractography may be more accurate with combinatorial strategies (Schilling et al., 2019). Although the present tractography findings may not be the exact representation of the overall streamlines between ROIs, the results were consistent within the presently investigated sample.

Moreover, a careful selection of ROIs, by taking into account the presence of white matter areas near them, makes it a powerful data-driven approach.

5. Conclusion

Using probabilistic tractography more streamlines were found between the piriform cortex and the thalamus in the left hemisphere suggesting a direct connection between the two ROIs. A positive correlation with intensity ratings for trigeminal odors appeared to reflect the role of the thalamus in mediating attention towards trigeminal properties of bimodal odors. There were also more streamlines between the piri-

form cortex and the OFC in the right hemisphere which largely confirms that the two structures are well connected. The positive correlation with threshold scores for trigeminal odors suggested the involvement of primary and secondary cortices in simple olfactory tasks. It would be interesting to see how such an analysis could be utilized in patients with olfactory dysfunction.

Data availability statement

The data that support the findings of this study are not publicly available. However, the authors will share them by request from any qualified investigator after completion of a data sharing agreement.

Declaration of Competing Interest

The authors declare no competing financial interests.

Credit authorship contribution statement

Divesh Thaploo: Formal analysis. **Akshita Joshi:** Formal analysis, Writing – review & editing. **Charalampos Georgiopoulos:** Formal analysis, Writing – review & editing. **Jonathan Warr:** Visualization, Project administration, Writing – review & editing. **Thomas Hummel:** Writing – review & editing, Methodology, Project administration, Supervision.

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