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Statistical localization of human olfactory cortex

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ABSTRACT

Functional neuroimaging methods have been used extensively during the last decades to explore the neural substrates of olfactory processing. While a general consensus on the functional anatomy of olfactory cortex is beginning to emerge, the mechanisms behind the functions of individual processing nodes still remain debated. Further, it remains unclear to which extent divergent findings result from differences in methodological approaches. Using Activation Likelihood Estimation (ALE), the aim of the present study was to statistically combine all published data on functional neuroimaging of olfaction to provide a probability map reflecting the state of the field to date. Additionally, we grouped studies according to various methodological approaches to investigate whether these systematically affected the reported findings. A total of 45 studies (69 contrasts, 594 foci) met our inclusion criteria. Significant ALE peaks for odor against baseline were observed in areas commonly labeled as primary and secondary olfactory cortex, such as the piriform and orbitofrontal cortex, amygdala, anterior insula, and ventral putamen. In addition, differences were observed in the extent to which different methods were able to induce activation in these different nodes of the olfactory network.

Introduction

Over the last 25 years, our understanding of basic sensory processing and neurobiological substrates of the human sense of smell has increased notably. This progress has in particular been facilitated by methodological advances in functional neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

While the substantial rise in the number of functional neuroimaging articles published on olfactory processing has contributed significantly to localization inferences of primary and secondary olfactory cortex, it has also brought considerable challenges to the scientific community. In particular, the diversity of methods and experimental paradigms, statistical analyses, and approaches to data interpretation often render between-study comparisons and the integration of findings a complex and evasive task. Considerable disagreement persists concerning the best approaches for studying olfactory mediated brain activations, and potential influences of these methodological differences on experimental results have not yet conclusively been investigated. In the following, we will provide a brief descriptive overview of the anatomy and connectome of the peripheral and central primate olfactory system. Within a meta-analytical context of published functional neuroimaging data, using the statistical activation likelihood estimation (ALE) method, we will then identify areas of the cortical olfactory network which are consistently activated across human neuroimaging studies, and quantify functional differences between frequently employed approaches.

The early portion of the olfactory sensory pathway has been well mapped out using neural tracing methods and anatomical studies in non-human animals. In primates, sensory processing of odors starts at the olfactory mucosa situated on the roof of the nasal cavity. Here, the odor molecules bind to the primary sensing cells, the olfactory receptor neurons. Their axons form the olfactory nerve, projecting to the tufted and mitral cells of the olfactory bulb (Firestein, 2001). From there, the largest portion of neuronal input is received by the piriform cortex. However, several other structures also receive direct projections from the olfactory bulb, including the anterior olfactory nucleus, the olfactory tubercle, a small anteromedial part of the enthorhinal cortex, the periamygdaloid cortex as well as several areas within the amygdala, including the anterior cortical nucleus and the nucleus of the lateral olfactory tract (Carmichael et al., 1994; Price, 1985). Together, these structures receiving direct input from the olfactory bulb have traditionally been labeled as olfactory cortex (Price, 2003).

Neuroanatomical and electrophysiological studies in primates consistently demonstrate that the areas traditionally labeled as primary olfactory sensory areas project to a secondary series of structures,

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including the caudal orbitofrontal cortex (OFC), the agranular insula, the hippocampus, but also the dorsomedial nucleus of the thalamus, medial and lateral hypothalamus, and ventral striatum and pallidum (Carmichael et al., 1994; Price, 2003). Among these, the region that receives the majority of corticocortical projections from the piriform cortex is the caudal OFC (Carmichael et al., 1994; Rolls et al., 1996), which as such has traditionally been considered to constitute secondary olfactory cortex. In addition to this direct link, this region also receives indirect projections from several areas of the primary olfactory cortex through a relay in the dorsomedial nucleus of the thalamus (Buck, 2000; Powell et al., 1965). Extensive projections subsequently connect the caudal OFC to other anatomical subsections of the orbitofrontal cortex (Price, 2003).

In contrast to this detailed structural understanding of the olfactory neural pathways, the functional contributions of the main processing nodes within the cortical olfactory network have only recently been systematically explored by means of functional neuroimaging techniques, and are to date far less coherently defined. Several reviews have attempted to offer a synthesis of the functional neuroimaging findings reported for the olfactory sense. These reviews have been either narrative (Gottfried, 2006; Royet and Plailly, 2004; Savic, 2002; Sela and Sobel, 2010; Yeshurun and Sobel, 2010; Zald and Pardo, 2000; Zelano and Sobel, 2005) or have made attempts to present the findings visually, plotting the activations reported in individual studies on the same anatomical template (Djordjevic and Jones-Gotman, 2006; Gottfried and Zald, 2005b; Zatorre and Jones-Gotman, 2000). While literature reviews are well suited to find common activations between studies based on a given variable of interest, much of the three-dimensional spatial information that voxel-based data consists of is lost. Function–location meta-analyses like ALE, on the other hand, merge data from many datasets to see whether consistent patterns arise that may not be evident on the basis of individual reports. By means of formal statistical integration of the available data, they are thus able to not only visualize common activation between studies, but also to provide a formal estimate of activation likelihood.

The goals of the present meta-analysis were twofold. First, we identified olfactory neuroimaging studies that were sufficiently similar in methodology to allow for their combination into a quantitative estimate of activation likelihood. This not only allowed us to increase our understanding of the regions commonly involved in the processing of olfactory information, but also, to provide the chemosensory imaging community with a probability map of the olfactory network that can be used as an independent inclusive mask in statistical analyses of future neuroimaging data. Second, we divided the included studies according to variations in experimental parameters to estimate their potential impact on the reported neural representation of odor processing. In particular, we assessed the effects of cued versus non-cued odor presentation, passive smelling versus active tasks, and among the passive smelling tasks, the difference between studies asking subjects to practice velopharyngeal closure (a technique minimizing subject-induced airflow through the nasal passages) and studies not instructing subjects to practice this technique. Finally, we investigated the effects associated with the restriction of the subject sample to male or female subjects only.

Method

Identification of papers

Suitable papers were identified by means of a two-step procedure. First, we searched the Medline and PsycINFO databases to identify human olfactory functional imaging journal articles either published or in press at the end of September 2012. Keywords used were *positron emission tomography* and *functional magnetic resonance imaging* (including common acronyms and synonyms such as *PET*, *fMRI*, *regional cerebral blood flow*, *BOLD*, etc.) which were cross-referenced with the search terms *odor**, *odour**, *olfact**, or *smell** using the wildcard option (asterisk in this case) to capture all possible endings of the terms. As a second step, the reference lists of the original research articles resulting from this search were explored using tools accessible in Web of Science to find additional articles that were not identified by the Medline and PsycINFO searches.

Inclusion criteria

The contrasts reported in the identified articles had to fulfill ten criteria to be included in the meta-analysis. 1) The stimulus had to be odorous only, i.e. no additional interacting stimuli such as tastants were allowed to be present. We did not, however, exclude contrasts of odorants that had the potential to activate both the olfactory and the trigeminal system, unless this was explicitly stated by the authors of the article. 2) The contrast had to be of an odorous stimulus contrasted against an 'odorless' baseline. Direct comparisons between two conditions both including olfactory processing were excluded. 3) We included contrasts regardless of the task performed by the subject during or after scanning. The inclusion of contrasts independent of task allows maximum benefits from the use of statistical probability methods. Activations not mediated by olfactory processing will be identified as outliers by the ALE analyses due to the inconsistency in their activations across studies. 4) The odorant stimulus had to be administered orthonasally. 5) Whole-brain data needed to be reported in a direct contrast, i.e. contrasts reporting only results of region of interest analyses (ROI), volume of interest analyses (VOI), or significant small volume corrections (SVC) were excluded. Also, studies that did not acquire signals from the whole brain, or reported only correlations of BOLD signal change with other measures, such as behavioral data, were excluded. 6) We only included contrasts of healthy young subjects, i.e. contrasts based on special populations, such as aged individuals, were excluded. 7) No more than five contrasts from any given study were included to avoid overrepresentation of one individual experiment (on average, 1.5 contrasts were included per study). 8) The article had to report all peaks and contain sufficient explanation of both experimental and control task to allow for a proper evaluation of the method. In case of missing information, studies were included if authors provided the missing methodological information via email. 9) Only results reported in a standardized stereotaxic space, i.e. MNI or Talairach space, were included. 10) We only included contrasts originating from group-based comparisons and not from single subject analyses. BOLD signal had to be acquired from, and averaged across, at least five subjects for the contrast to be included. Deactivations were omitted due to the infrequency with which they are reported, and contrasts using between-group comparisons were omitted because they do not allow for a separation of group- and odor-dependent effects.

Procedure and statistical calculations

All analyses were performed using the Java-based version of the ALE software (GingerALE 2.2; http://www.brainmap.org/ale), an automated analysis software that has been described in detail elsewhere (Eickhoff et al., 2009; Eickhoff et al., 2012; Laird et al., 2005; Turkeltaub et al., 2002; Turkeltaub et al., 2012). In brief, one of the major benefits of this method compared to many others is that ALE analyzes the given coordinates to search for concordance, modeling each of the reported foci as the center of a 3D Gaussian probability distribution by permutation testing. These distributions are then used to create a whole-brain statistical map that estimates the likelihood of activation for each individual voxel as determined by the entire set of studies included (Laird et al., 2005). As a first step prior to statistical analyses, the anatomical template used for group statistics in each included article was noted. Using the GingerALE transformation tool, the reported coordinates were then transformed from their original template space into MNI space to ensure that all data