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DISSOCIATED NEURAL REPRESENTATIONS INDUCED BY COMPLEX AND SIMPLE ODORANT MOLECULES

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Abstract—An important challenge in olfaction research is to understand how percepts relate to the molecular structure of stimuli. Previous psychophysical studies showed that, whereas structurally simple odorant molecules evoked a more uniform qualitative perception as revealed by the use of a small number of labels to describe their olfactory quality, more complex odorants evoked a larger variety of olfactory qualities, reflecting a more heterogeneous qualitative perception. The present study examined how this influence of odorant molecular complexity on perception is reflected in the human brain. To this end, participants were stimulated with structurally simple and complex odorant molecules and their brain responses were assessed by functional magnetic resonance imaging (fMRI). Low- and high-complexity odorants were judged to have the same intensity, pleasantness and familiarity ($p > 0.05$ in all cases), whereas complex odorants induced more quality labels than simple odorants ($p < 0.02$) as expected. Imaging analysis of complex vs. simple odorants revealed significant activation in dorsal anterior cingulate gyrus, but not in primary olfactory areas. Taken together, these findings suggest dissociated neural representations of uniform and heterogeneous olfactory perception, highlighting for the first time the impact of odorant complexity on activity of the cingulate gyrus.

Key words: olfaction, perception, molecular structure, molecules, fMRI.

INTRODUCTION

In the auditory and visual systems, the physical properties of sensory stimuli are predictive of perception: the pitch of a sound is perceived as high or low depending on its acoustic frequency, and perceived colors derive from the integration of light-wave frequencies. In olfaction, however, the link between stimulus properties and perception is not totally understood. For example, how perceived intensity can be predicted from molecular properties of an odorant (related to its volatility, hydrophobicity, etc.) remains to be elucidated (Mainland et al., 2014). Regarding odor quality, perfumers and chemists noticed that the presence of certain chemical groups in a given odorant molecule was often associated with specific olfactory qualities (Arctander, 1994; Chastrette, 2002). For example, molecules containing chemical groups such as esters are often described as having a fruity note. In spite of this, it remains difficult to predict the olfactory quality of an odor source based solely on its chemical composition, especially for complex odors (such as food aromas; see for example Baldwin, 2002).

Previous investigations attempted to relate odor quality to the odorant's physicochemical parameters (Amoore, 1964; Schiffman, 1974; Khan et al., 2007; Mandairon et al., 2009; Haddad et al., 2010; Poncelet et al., 2010; Joussain et al., 2011; Zarzo, 2011). For instance, Kermen and colleagues (2011) showed a relationship between the complexity of odorant structure and odor perception. Molecular complexity was quantified with an index of how complicated a molecular structure is, based on bond connectivity, diversity of non-hydrogen atoms, and symmetry (Hendrickson et al., 1987). Specifically, it was shown that, whereas structurally simple odorant molecules evoked a more uniform qualitative perception as revealed by the use of a small number of labels to describe their olfactory quality, more complex odorants evoked a larger variety of olfactory qualities, reflecting a more heterogeneous qualitative perception. The present study set out to examine how this influence of molecular complexity of odorants on this form of "olfactory polysemy" is reflected in the human brain.

Previous studies showed that piriform cortex, entorhinal cortex, amygdala, prefrontal and cingulate gyri are involved in olfactory processing (Sobel et al., 2000; Zatorre et al., 2000; Gottfried et al., 2002; Anderson et al., 2003; Herz et al., 2004; Kareken et al., 2004; Savic and Berglund, 2004; Small et al., 2005; Plailly et al., 2007; Bensafi et al., 2008, 2012, 2014; Reske et al., 2010; and for detailed reviews of anatomy

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Abbreviations: EPI, echo planar imaging; fMRI, functional magnetic resonance imaging; GUA, Guaiacol; ISO, Isoamyle acetate; LIM, D-Limonene; SEM, standard error of the mean; TE, Time to Echo; TER, Terpinen-4-ol; TR, Time to Repetition.

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and functions of the olfactory system, see Price, 1990; Lundström et al., 2011). In the present study, analyses thus focused on these central areas, with two specific hypotheses. The first hypothesis concerns the piriform cortex. In a series of experiments, Gottfried and colleagues sought to determine whether this area encoded information about olfactory quality (Gottfried et al., 2006; Howard et al., 2009). To this end, they used odorants that varied in quality (lemon-like and vegetable-like) in a cross-adaptation paradigm. Their results revealed the posterior part of the piriform cortex responded to variation in olfactory quality, and that a given olfactory quality induced a specific pattern of activation in this area. Therefore, one may expect that complex odorants would induce a larger response in this brain area due to their potential to evoke a greater diversity of perceived qualities than simple odorants (Kermen et al., 2011). The second hypothesis involves frontal and cingulate areas. Because olfactory polysemy associated with complex odorant molecules may induce conflict or competition between the multiple evoked qualities, we hypothesized that activity in areas such as the inferior frontal gyrus and the cingulate gyrus would be larger in response to complex odorant molecules. These areas have been shown to be more activated during tasks involving a higher level of competition generated by ambiguous semantic information (Bilenko et al., 2009) and the anterior cingulate cortex is known to respond to the occurrence of cognitive conflict (Botvinick et al., 2001, 2004).

To this end, two experiments were conducted. First, in a pilot experiment we aimed at testing whether the preselected simple and complex odorants differed as expected in the number of descriptors evoked when perceived. This pilot also examined whether the odorants differed on a series of perceptual dimensions (such as pleasantness or intensity). Second, the main experiment combined psychophysics and functional magnetic resonance imaging (fMRI) in a within-subject design. Brain activations related to perception of the odorants used in the pilot study, i.e. with low and high molecular complexity, were measured. To rule out potential effects of other perceptual dimensions, participants were required to rate stimulus intensity, pleasantness and familiarity for all stimulus conditions.

EXPERIMENTAL PROCEDURES

Participants

The participants were 21 right-handed volunteers (mean M ± standard deviation SD 23.3 ± 2.2 years old; four men). They received financial compensation for the time spent in the laboratory. The recording procedure was explained in great detail to the participants, who provided written consent prior to participation. The study was conducted according to the Declaration of Helsinki and was approved by the ethics committee of the University of Dresden (application number EK 334102010). Detailed medical history combined with ENT endoscopic examination of the nasal cavity and odor perception assessment by the ‘‘Sniffin’ Sticks’’ test (Hummel et al., 1997) ascertained that participants were in good health and had a normal sense of smell.

Stimulus selection and pilot experiment

Based on a previous psychophysical study (Kermen et al., 2011), we selected two complex odorants (D-Limonene, LIM, and Terpinen-4-ol, TER; complexity values: 163 and 170 respectively) and two simple odorants (Isoamyle acetate, ISO, and Guaiacol, GUA; complexity values: 86.9 and 83 respectively). In Kermen et al.’s study, the complexity of the odorants was collected from PubChem (http://pubchem.ncbi.nlm.nih.gov/), computed using bond connectivity, diversity of non-hydrogen atoms and symmetry of the molecule, according to a formula detailed elsewhere (see Hendrickson et al., 1987; Kermen et al., 2011). Here, odorant selection was based on the fact that (i) the complex odorants LIM and TER evoked a greater number of semantic associations per participant than the simple odorants ISO and GUA (mean M ± standard error of the mean SEM: 0.29 ± 0.06 vs. 0.15 ± 0.05 respectively; $p < 0.03$ one-tail test) in Kermen et al.’s free verbal task, and (ii) the complex odorants LIM and TER did not differ from the simple odorants ISO and GUA for pleasantness (4.8 ± 0.26 vs. 4.92 ± 0.27, $p > 0.05$), familiarity (5.12 ± 0.38 vs. 5.73 ± 0.28, $p > 0.05$), intensity (5.85 ± 0.20 vs. 6.02 ± 0.22, $p > 0.05$), and edibility (3.73 ± 0.26 vs. 3.95 ± 0.23, $p > 0.05$). The odorants were provided by Sigma–Aldrich and were diluted in propylene glycol to obtain iso-intense perception (in vol/vol concentration: LIM 35%, TER 10%, ISO 0.65%, GUA 2.5%).

As can be seen from the above, free verbal elaboration tasks in olfactory studies result in a very low number of descriptors (on average, participants generated 0.22 labels per odor in Kermen et al., 2011). In the present study, to circumvent this problem and help participants describe odors, we set up a list of descriptors to choose from. To constitute this list, we firstly looked at how the four selected odors were described in the Arctander atlas, a book commonly used in the fields of chemistry, perfumery and olfaction (Arctander, 1994). From this examination, we selected six generic descriptors: three with a rather positive hedonic valence (fruity, peppery, and woody) and three with a rather negative valence (smoky, medicinal, and earthy). Secondly, to enlarge the description list, we selected 10 additional descriptors from the more detailed Dravnieks atlas (Dravnieks et al., 1985), half with a positive hedonic value and half with a negative one (based on Dravnieks et al., 1984). These were (in parentheses: descriptor hedonic value on a scale ranging from −5 to +5): minty (2.5), floral (2.39), herbaceous (2.14), buttery (2.04), spicy (1.99), alcohol (−0.47), metallic (−0.94), animal (−1.13), solvent (−1.16) and oily (−1.41). Thus, the final list, used in the pilot and the main study, is constituted of 16 odor qualities: alcohol, animal, buttery, earthy, floral, fruity, herbaceous, medicinal, metallic, minty, oily, peppery, smoky, solvent, spicy, and woody.

To ensure that simple and complex odorants used in this study did evoke different numbers of qualities, but did not differ in other olfactory and trigeminal