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Olfactory training induces changes in regional functional connectivity in patients with long-term smell loss

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ABSTRACT

Recently, olfactory training has been introduced as a promising treatment for patients with olfactory dysfunction. However, less is known about the neuronal basis and the influence on functional networks of this training. Thus, we aimed to investigate the neuroplasticity of chemosensory perception through an olfactory training program in patients with smell loss.

The experimental setup included functional MRI (fMRI) experiments with three different types of chemosensory stimuli. Ten anosmic patients (7f, 3m) and 14 healthy controls (7f, 7m) underwent the same testing sessions. After a 12-week olfactory training period, seven patients (4f, 3m) were invited for follow-up testing using the same fMRI protocol. Functional networks were identified using independent component analysis and were further examined in detail using functional connectivity analysis.

We found that anosmic patients and healthy controls initially use the same three networks to process chemosensory input: the olfactory; the somatosensory; and the integrative network. Those networks did not differ between the two groups in their spatial extent, but in their functional connectivity. After the olfactory training, the sensitivity to detect odors significantly increased in the anosmic group, which was also manifested in modifications of functional connections in all three investigated networks.

The results of this study indicate that an olfactory training program can reorganize functional networks, although, initially, no differences in the spatial distribution of neural activation were observed.

1. Introduction

Anosmia, the complete loss of the ability to perceive odors, is a common disorder that has wide-ranging effects on everyday life (for review see Croy et al., 2014). However, treatment options for patients with olfactory dysfunction are still limited. Recently, a new and promising treatment option for patients who suffer from smell loss was developed — olfactory training (Hummel et al., 2009a). In a large multicenter study, olfactory training was proven successful, especially in patients with olfactory dysfunction following an upper respiratory tract infection (Damm et al., 2014). Previous studies revealed not only an increase in smell performance induced by an olfactory training program in patients with olfactory dysfunction, but also showed a neural plasticity effect (Kollndorfer et al., 2014). Before the training, the authors found a diverse network of functional connections for the piriform cortex that involved a broad range of non-olfactory brain areas. After training, these connections declined, suggesting the reorganization of functional connections of the piriform cortex induced by the olfactory training. However, the effect of olfactory training on processing pathways of chemosensory stimuli remains unclear.

The olfactory processing pathway is unique among our senses, as every form of chemosensory perceptional input is a result of an interaction between the olfactory and the trigeminal systems. This processing partnership has several reasons: the olfactory system is responsible for odor quality perception, whereas the trigeminal system conveys sensations in the nasal cavity, such as stinging, burning, temperature, or pain. In addition, the trigeminal system provides an important warning system to protect the airways from harm (Hummel et al., 2003, 2009; Kleemann et al., 2009). Results of functional imaging studies have shown the interaction between the olfactory and the trigeminal

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systems on a cerebral level, as trigeminal stimulation activates pain processing areas, such as the insula, the anterior cingulate cortex, or the primary somatosensory cortex (Bensafi et al., 2008; Iannilli et al., 2008, 2007), as well as olfactory-related areas, such as the orbitofrontal cortex (Albrecht et al., 2010). The close interaction of these two systems is of immense interest in patients with olfactory disorders. Patients who suffer from anosmia – the complete loss of the sense of smell – therefore lose the connection to one of the 'cerebral partners' that process chemosensory information, while the other partner continues to function. Frasnelli et al. (2010) have shown that trigeminal perception is reduced in patients with olfactory dysfunction.

The present study was designed to address the following aims. First, we aimed to investigate the specificity and sensitivity of the chemosensory system in patients with anosmia. The second aim was to investigate the effect of olfactory training on the chemosensory processing networks. These research aims were targeted on an fMRI experiment involving different chemosensory stimuli. To investigate the specific alterations of the chemosensory system (aim 1), three compounds were chosen to evoke various sensations in the nasal cavity: 1) carbon dioxide (CO_2), which is perceived as completely odorless and creates a burning and stinging sensation; 2) menthol, which is perceived as a fresh odor, and evokes a cooling sensation in the nose; and 3) cinnamaldehyde, which smells like cinnamon and causes a warm sensation. These three trigeminal compounds differ in three domains: First, all three compounds target different trigeminal receptor subfamilies. CO_2 activates the TRPV1 receptor (Julius et al., 1997), menthol stimulates the TRPM8 receptor (Peier et al., 2002), and cinnamaldehyde targets the TRPA1 receptor (Bandell et al., 2004). Second, they evoke distinct sensations in the nose. And third, CO_2 is perceived as odorless, whereas menthol and cinnamaldehyde have a clear olfactory quality. The diversity of functional connectivity in networks that process different chemosensory inputs was tested in healthy controls and in patients with anosmia, based on the three chemosensory compounds. For the second aim, neuronal as well as olfactory performance modifications, induced by olfactory training in the anosmic patient group, were investigated. To test this, patients with long-term smell loss due to infection underwent the fMRI experiment before and after a 12-week olfactory training period. We hypothesized that training induces alterations of functional connectivity in olfaction-related networks.

2. Materials and methods

All experiments in this study were approved by the Ethics Committee of the Medical University of Vienna. All subjects were informed about the aims of the study and gave their written, informed consent prior to inclusion.

In this study, we performed two experiments (see Fig. 1), which are described in detail in the following paragraphs.

2.1. Experiment 1

Experiment 1 included two cohorts of subjects, healthy control subjects and patients with anosmia. Nineteen healthy subjects (ten female, nine male) participated. All healthy subjects had normal olfactory function and had no history of neurological or psychiatric diseases. Five subjects had to be excluded from further processing due to incomplete fMRI measurements. Fourteen subjects (seven female, seven male; mean age, 30.1 years; SD, 6.7) completed all measurements and underwent further analysis. For the second cohort, 11 patients with smell loss after an upper respiratory tract infection were screened. One anosmic patient had to be excluded from the data set due to incomplete fMRI measurements, resulting in a total of 10 patients with smell loss (seven female, three male; mean age, 43.4 years; SD 14.1), with a mean disease duration of 4.1 years (SD 3.0), who were then included in the final analysis. All anosmic patients were examined by an ENT, which included an endoscopic examination of the nasal cavity, to determine the cause of olfactory dysfunction. To prevent any influence of trauma-induced alterations of functional brain networks, only patients diagnosed with anosmia after an infection of the upper respiratory tract, were included in this study. Further measurements of olfactory function, as described below, were performed to assess the severity of olfactory dysfunction (Kobal et al., 2000).

All participants completed three scanning sessions, one for every stimulus: 1) CO_2 (50% v/v); 2) cinnamaldehyde (75% v/v dissolved in 1,2-propanediol; Sigma Aldrich, Germany); and 3) menthol (2.5 g; Sigma Aldrich, Germany). Chemosensory stimuli were delivered in an event-related design, using a computer-controlled, air-dilution olfactometer compatible with magnetic resonance imaging (MRI), which was constructed at the Center for Medical Physics and Biomedical

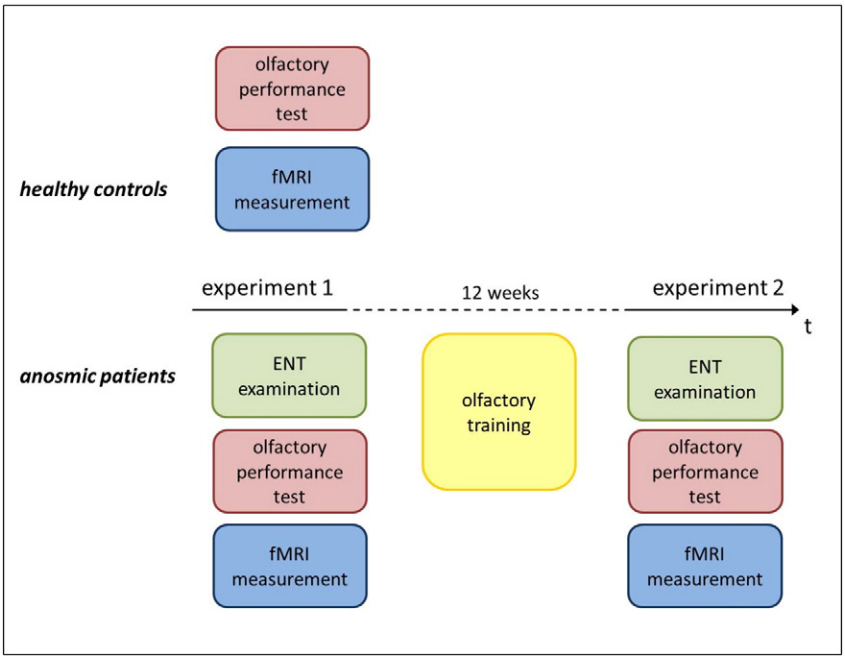

Fig. 1. Schematic description of experimental procedures.