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Neural correlates of taste perception in congenital olfactory impairment

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ABSTRACT

Olfaction and gustation contribute both to the appreciation of food flavours. Although acquired loss of smell has profound consequences on the pleasure of eating, food habits and body weight, less is known about the impact of congenital olfactory impairment on gustatory processing. Here we examined taste identification accuracy and its neural correlates using functional magnetic resonance imaging (fMRI) in 12 congenitally olfactory impaired individuals and 8 normosmic controls. Results showed that taste identification was worse in congenitally olfactory impaired compared to control subjects. The fMRI results demonstrated that olfactory impaired individuals had reduced activation in medial orbitofrontal cortex (mOFC) relative to normosmic subjects while tasting. In addition, olfactory performance as measured with the Sniffin' Sticks correlated positively with taste-induced blood-oxygen-level dependent (BOLD) signal increases in bilateral mOFC and anterior insula. Our data provide a neurological underpinning for the reduced taste perception in congenitally olfactory impaired individuals.

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1. Introduction

Our appreciation of fine foods or drinks largely comes from a rich diversity of flavours perceived mainly by our sense of smell, together with taste (e.g. sweet, salty) and trigeminal (e.g. temperature, texture) sensations (Auvray & Spence, 2008; Lundstrom, Boesveldt, & Albrecht, 2011). The loss of olfaction has therefore strong repercussions on flavour perception but it remains unclear how this is manifested at the cerebral level. Studies have demonstrated that the olfactory and gustatory systems largely overlap. Following activation of taste receptors, taste information travels from the VII, IX and X cranial nerves to reach first the nucleus of the solitary tract of the brainstem, followed by the ventral posterior medial nucleus of the thalamus and then converges towards the primary and secondary taste cortices in the insula/operculum and orbitofrontal cortex (OFC), respectively (Sewards, 2004). Smell information, on the other hand, is conveyed by the olfactory nerve (I) and synapses first in the olfactory bulb before reaching the

piriform and entorhinal cortices (primary olfactory cortices), followed by various higher order olfactory areas such as the amygdala, cingulate cortex, insula and orbitofrontal cortex. According to the traditional view, taste-odour integration occurs in the orbitofrontal cortex (Rolls, 2001, 2008; De Araujo, Rolls, Kringelbach, McGlone, & Phillips, 2003) and insula (Small & Prescott, 2005; Verhagen & Engelen, 2006). However, recent evidence from rodent studies challenges the classical view (Small, Veldhuizen, & Green, 2013) as taste neurons were also recorded within the posterior piriform cortex (Maier, Wachowiak, & Katz, 2012). This close anatomical relationship between olfactory and gustatory systems suggests that odour impairments may affect the central processing of taste.

Odour impairments are common and affect nearly 5% of the population (Karstensen & Tommerup, 2011). Acquired anosmia resulting from traumatic brain injury, infection of the upper respiratory tract or other diseases leads to a decreased appetite and lower interest in eating, changes in body weight, disturbances in affective behaviour (e.g. depression), and a reduced quality of life (Ferris et al., 1985; Mattes & Cowart, 1994; Van Toller, 1999; Miwa et al., 2001; Temmel et al., 2002; Aschenbrenner et al., 2008). In addition, these patients display decreases in gustatory (Gudziol, Rahneberg, & Burkert, 2007) and trigeminal (Gudziol, Schubert, & Hummel, 2001; Frasnelli, Schuster, & Hummel, 2010)

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sensitivity. At the cortical level, brain imaging studies on trigeminal processing using event-related potentials (Frasnelli, Schuster, & Hummel, 2007a) and functional magnetic resonance imaging (fMRI; Iannilli, Gerber, Frasnelli, & Hummel, 2007) in patients with acquired anosmia compared to controls revealed lower activity in chemosensory brain areas, such as the right somatosensory cortex and left insula (Iannilli et al., 2007).

In contrast to acquired anosmia, the consequences of congenital absence of smell on eating habits and flavour processing have received little attention. The few published studies failed to observe differences in eating patterns or electrogustatory and trigeminal sensitivity in individuals with isolated congenital anosmia (Frasnelli, Schuster, & Hummel, 2007b; Croy, Negoias, Novakova, Landis, & Hummel, 2012) or Kallmann syndrome (Hasan, Reddy, & Barsony, 2007). In sharp contrast, Levy and colleagues (2013) found that nearly half of their congenitally anosmic patients had lower taste detection and taste identification thresholds compared to normosmics, indicating that life-long olfactory deprivation can have a negative effect on taste function.

Here, we investigated taste perception in a cohort of otherwise healthy participants with isolated congenital olfactory impairment (COI). All participants had close relatives also affected with isolated COI, indicating a genetic pre-disposition of the disorder. Their symptoms could not be ascribed to Kallmann syndrome or other known genetic syndromes, in which olfactory impairment is part of a larger clinical picture with various other symptoms. COI patients are particularly interesting because of their life-long absence of odour perception that may have changed the maturation of brain pathways and triggered crossmodal neuroplastic rearrangements. The goal of the present fMRI study was to test whether COI tasting impairments are related to altered BOLD responses in gustatory- and olfactory-processing brain areas. Our main region of interest (ROI) was the medial orbitofrontal cortex (mOFC), as this region is the classical area where taste and smell information are combined into a flavour percept (De Araujo et al., 2003). The anterior insula and the piriform cortices (Small & Prescott, 2005; Maier et al., 2012; Small et al., 2013) were considered as secondary ROIs.

2. Methods

2.1. Participants

Twenty-five right-handed (Edinburgh handedness inventory; Oldfield, 1971) subjects participated in the fMRI experiment. Within the affected group of individuals (COI), 3 were from a Danish family and the remaining were Faroese and mixed Danish and Faroese origin. Gender and age-matched normosmic control subjects were recruited from the Faroese family cohort and from the Faroese community living in the Copenhagen area through advertising.

All subjects with COI reported to have a life-long inability to smell. Subjects living in the Faroe Islands or Denmark were examined by an otolaryngologist at the National hospital of the Faroe Islands or at the Vejle hospital in Denmark. The examination procedure included laryngoscopy of the nose and throat, a clinical interview with questions related to their history of olfactory dysfunction, head trauma, employment and pubertal development. Two subjects were excluded based on either childhood head trauma or chronic nasal infection. For the remaining sample, no other associated neuropathies could be related to the loss of smell. Demographic data of the subjects are given in Table 1a.

A trained radiologist assessed the T_1-weighted, T_2-weighted and FLAIR images for pathologies in the brain, nasal cavity, sinuses or nasal mucosa. This inspection led to the removal of one COI participant. Another COI subject was also removed from the fMRI analysis because of technical scanning problems. One control participant that showed presbyosmia related to age (62 years old) was excluded from the analysis to avoid heterogeneity within the otherwise normosmic control group (NC; $n=8$; 4 females).

The groups were matched in terms of age, sex, body mass index (BMI), education and cognitive function (MoCA©) (Table 1b). Experiments were performed at the Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital Hvidovre in Denmark. The research ethics committee of the Faroe Islands

[200812] and the capital region of Denmark approved the study [H-A-2009-063, 28963] and all subjects gave informed and written consent prior examination.

2.2. Olfactory Assessment

Examination of olfactory ability was done at the Danish Research Center for Magnetic Resonance, at Hvidovre Hospital, Denmark. We used the Sniffin' Sticks threshold-discrimination-identification (TDI) score (Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997; Hummel, Kobal, Gudziol, & Mackay-Sim, 2007; Table 1a) and history of odour perception, head trauma as well as medical and psychiatric illness obtained from the semi-structured interviews to exclude psychopathology and classify the participants into congenitally olfactory impaired (COI; TDI < 30.3; Hummel et al., 2007) and normosmic control (NC; TDI > 30.3) groups. All participants were also tested for phenylthiocarbamide (PTC) sensitivity using taste strips (Fisher scientific).

2.3. MRI data acquisition

Subjects were scanned using a 3-T Siemens Magnetom Verio MR scanner (Siemens, Erlangen, Germany) equipped with a 32-channel head coil (Invivo, FL, USA).

We collected single shot gradient echo-planar images (EPI) covering the whole-brain with BOLD contrast in an oblique orientation to the commissural plane (TR/TE of 2,15 s/ 26 ms, 78° flip angle, 64×64 matrix, FoV of 192×192 mm^2, 42 slices with no gap, 3 mm thickness, $3 \times 3 \times 3$ mm^3 voxels). In each of the two functional sessions, 197 dynamic scans were acquired. Head motion was restricted with comfortable padding around the participant's head.

2.4. Stimuli and stimulation equipment

Three different tastants: sweet (sucrose; 0.028 M), salty (sodium chloride; 0.16 M), bitter (quinine hydrochloride; 0.024 mM) and solvent (deionised water) were prepared for the fMRI sessions. During scanning, tastants were manually delivered at a rate of 3 mL / 3 s, using a homemade gustometer consisting of a mouthpiece attached to syringes (60 mL) through separate tubing (length of 1.7 m; diameter of 3 mm). A 3 mL volume of water was administered after each tastant to rinse the subject's mouth. All liquids were swallowed during scanning.

2.5. Experimental fMRI procedure

Participants underwent two fMRI runs with 25 stimulus presentations per run, resulting in a total of 50 stimulus presentations. In both runs, every tastant (sweet, salty and bitter) was administered 5 times whereas the control condition (water, solvent) was repeated 10 times, all presented in a pseudo-randomized fashion. As illustrated in Fig. 1, the 3-s stimuli were separated by an inter-stimulus interval varying between 16 and 23 s. A visual warning cue ("Ready") presented on a retro projection screen indicated that the delivery of the tastant was imminent. At the same time, the experimenter received an auditory cue (MR Confon system) that informed him of the nature of the tastant. During stimulus delivery, he heard a count-down ("3-2-1-stop") and manually pushed the plunger of a syringe at a relatively constant flow of 3 mL / 3 s. Following tastant delivery, a second visual cue ("Answer") required the participant to indicate, in a forced-choice paradigm, the nature of the stimulus ("Sweet, Salty, Bitter, Water"; projected on the default screen display) using a computer-mouse key. The average time between the end of stimulus delivery and the response cue was 3 s, with a jitter from 0 to 6 s. Participants were asked to keep the fluid in their mouth until the swallow cue ("Swallow", appeared 3 s). Immediately after, 3 mL of water was administered to rinse the mouth ("Water", appeared 3 s), which was followed by the second "Swallow" cue signalling participants to swallow again. The mean total duration of each run was 488 s. Participants were instructed to swallow only when the swallow cue appeared, as swallowing can elicit important head movement. Respiratory motion was recorded throughout scanning with a respiration belt sampled at 50 Hz.

Following the fMRI session, participants were asked to recall the 3 tastants and rate their intensity and pleasantness on a 5-point rating scale with "1" as not perceptible or not pleasant and "5" as very strong or very pleasant.

2.6. Statistical analysis of the behavioural data

Based on the subjects' responses from the taste identification task, we calculated the number of hits, misses, false alarms and correct rejections. These measures were combined to estimate the sensitivity index d-prime following the signal detection theory method (Swets, 1961). A high d-prime indicates a good identification accuracy and a readily detected signal compared to noise. All variables were first assessed for normality using the Shapiro–Wilk test. To test for group differences in taste perception, we conducted 3 ANCOVAs with group (COI and NC) as independent variable, and the 3 tastes d-primes as dependant