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Research report

Peripheral adaptive filtering in human olfaction? Three studies on prevalence and effects of olfactory training in specific anosmia in more than 1600 participants

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ABSTRACT

Selective processing of environmental stimuli improves processing capacity and allows adaptive modulation of behavior. The thalamus provides an effective filter of central sensory information processing. As olfactory projections, however, largely bypass the thalamus, other filter mechanisms must consequently have evolved for the sense of smell. We investigated whether specific anosmia – the inability to perceive a specific odor whereas detection of other substances is unaffected – represents an effective peripheral filter of olfactory information processing.

In contrast to previous studies, we showed in a sample of 1600 normosmic subjects, that specific anosmia is by no means a rare phenomenon. Instead, while the affected odor is highly individual, the general probability of occurrence of specific anosmia is close to 1. In addition, 25 subjects performed daily olfactory training sessions with enhanced exposure to their particular "missing" smells for the duration of three months. This resulted in a significant improvement of sensitivity towards the respective specific odors.

We propose specific anosmia to occur as a rule, rather than an exception, in the sense of smell. The lack of perception of certain odors may constitute a flexible peripheral filter mechanism, which can be altered by exposure.

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1. Introduction

Selective processing of environmental stimuli facilitates adaptive modulation of behavior and improves processing capacities by focusing on relevant information. Filtering mechanisms can be divided into peripheral and central ones. Peripheral filters depend on the receptive properties of sensory cells. Human auditory hair cells, for instance, do not respond to ultrasound very well, shielding our ears from such acoustic input. Another example is the variation of receptor density of tactile nerves in different parts of the body, which, for example, provides very high discrimination ability in the fingertips. Such peripheral filters work similarly but also rather uniformly within a given species. Central filter mechanisms, on the other hand, are much more flexible. They are based upon complex top–down interactions, allowing precise attenuation of selective attention in accordance with the needs of the body. The thalamus is commonly regarded as the bottleneck of central sensory information processing, representing a relay that gates sensory information to the cerebral cortex in wakefulness while suppressing this flow of information during sleep for instance. Thalamic gating and thalamic-cortical loops focus attention. Furthermore, thalamo-cortical pathways are involved in sleep-to-wake transitions if significant environmental stimuli occur (McCormick & Bal, 1994). In olfaction, however, which evolutionarily preceded thalamic evolvement, the thalamus is largely bypassed and cannot operate as a gating agent. Some other phylogenetically ancient filter mechanisms should consequently be available for the sense of smell and might still be conserved in humans. Some of the gating functions otherwise performed by the thalamus are executed by the olfactory bulb (Kay & Sherman, 2007).

We investigated whether specific anosmia, the puzzling condition of being unable to perceive a specific odor in otherwise normal olfactory function, represents an effective peripheral filter of olfactory information processing.

Some of the first systematic descriptions of specific anosmia, also known as partial anosmia or odor blindness, extend back to 1893, where individuals were described who were able to smell all odors except vanilla [(Reuter, 1893) cited by (von Skramlik, 1926)]. Since that time it has been considered a rather rare phenomenon with a prevalence of as little as .1% for skunk smell (butyl mercaptan), for instance (Patterson & Lauder, 1948). In numerous studies, the rate of specific anosmia depended on the odor investigated: Specific anosmia to isovaleric acid, with a low molecular weight, varies between 2 and 3% (Whissel-Buechy & Amoore, 1973) (Amoore, 1977), whereas the prevalence of specific anosmia towards the larger molecules of pentadecalactone varies between 7 and 12% (Amoore, 1977; Whissel-Buechy & Amoore, 1973).

Research on specific anosmia was very active until the late 1970s. However, after the exciting first findings, results became more predictable: For nearly all tested odors, some specific anosmics could be identified. Thus, each odor needed to be tested in numerous subjects in order to capture the relatively small prevalence rate – apparently, as long as enough subjects were tested, there would be always some specific anosmia to any odor. Up to now, specific anosmias have been reported for about 60 odorants [for example see (Amoore, 1967; Hirth, Abadanian, & Goedde, 1986; Kirk & Stenhouse, 1953; Patterson & Lauder, 1948; von Skramlik, 1926; Triller et al., 2008; Whissel-Buechy & Amoore, 1973)], and presumably many more would emerge if that line of research were more active. At least 2467 active chemicals with an odor have been described (Arctander, 1969). If indeed almost all smells are possible targets of specific anosmias, and if the overlap of specific anosmia is rather low, it seems plausible that everybody should have a specific anosmia to some odor. As a consequence, while the frequency of anosmia to any single odor is rather small, the general phenomenon of specific anosmias seems quite normal: Specific anosmia might be considered to be the rule, rather than the exception of olfactory processing. There are some publications supporting this view: The prevalence of specific anosmia to at least one out of six odors was reported to be as high as 45% (Hirth et al., 1986), and the prevalence of specific anosmia to at least one out of 10 odors as high as 60% (Triller et al., 2008). A rather liberal definition of non-perception in those studies may have led to an overestimation of prevalences, but the basic notion remains to be taken seriously: the likelihood of being anosmic to any odor out of a large number is much higher than the probability to suffer from specific anosmia to one particular odor.

Among other factors, specific anosmia may be due to a change in secretion and composition of the mucus on the olfactory epithelium and expression of olfactory receptors. A mucus-related change in perception of odors may affect certain groups of molecules more than others, e.g., in relation to lipophilicity. The lack of certain receptors on the other hand results in specific anosmia for any odor that is mainly coded by the respective receptors. In theory, humans may be able to differentiate between as many as one trillion smells (Bushdid, Magnasco, Vosshall, & Keller, 2014), which are encoded from a relatively small number of different olfactory receptors, coded by about 400 functional olfactory receptor genes (Glusman, Yanai, Rubin, & Lancet, 2001). However, only some of the olfactory receptor genes are expressed. Examination of anatomical sections from 26 donators recently showed that humans on average express only about 26% of the olfactory receptor genes (range 18–51%), and so far the underlying selection process – that is, which olfactory receptors are expressed and which are not – is unknown (Verbeurgt et al., 2014). This apparently normal lack of olfactory receptors makes specific anosmia to some odors in any person likely. In addition, animal studies have revealed that receptors of the mouse nasal mucosa undergo regeneration approximately every 1–4 months (Graziadei & Monti-Graziadei, 1978). This could engender slow adaptation to the olfactory environment by adjusting olfactory receptor gene expression to the requirements of the individual. Such changes could, for instance, be triggered by learning or by hormonal changes (Chopra, Baur, & Hummel, 2008).

A methodological issue in specific anosmia research concerns the cutoff criterion. Odors typically bind to more than one receptor: olfaction is accordingly based on pattern recognition. As a consequence, non-expression of specific receptors will not lead to total non-perception of an odorous molecule as long as bindings to other receptors are preserved.