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Review

Habituation and adaptation to odors in humans

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ABSTRACT

Habituation, or decreased behavioral response, to odors is created by repeated exposure and several detailed characteristics, whereas adaptation relates to the neural processes that constitute this decrease in a behavioral response. As with all senses, the olfactory system continually encounters an enormous variety of odorants which is why mechanisms must exist to segment them and respond to changes. Although most olfactory habitation studies have focused on animal models, this non-systematic review provides an overview of olfactory habituation and adaptation in humans, and techniques that have been used to measure them. Thus far, psychophysics in combination with modern techniques of neural measurement indicate that habituation to odors, or decrease of intensity, is relatively fast with adaptation occurring more quickly at higher cerebral processes than peripheral adaptation. Similarly, it has been demonstrated that many of the characteristics of habitation apply to human olfaction; yet, evidence for some characteristics such as potentiation of habituation or habituation of dishabituation need more support. Additionally, standard experimental designs should be used to minimize variance across studies, and more research is needed to define peripheral-cerebral feedback loops involved in decreased responsiveness to environmental stimuli.

1. Introduction

Thompson and Spencer determined in the late 60s the nine behavioral principles of habituation in a landmark paper [89], and these principles were repeated and expanded upon by Groves and Thompson in 1970 [30]. In 2009, Rankin and colleagues revisited and refined the characteristics of habituation based on a wide variety of animal species, resulting in the final definition of habituation with an additional principle that is used today [69]. According to Rankin, "habituation is defined as a behavioral response decrement that results from repeated stimulation and that does not involve sensory adaptation/sensory fatigue or motor fatigue." This definition comes from traditional animal studies where observed behaviors were reduced, and does not encompass underlying processes that create such behavioral changes, as a decrease of a perception or of a sensation. Therefore, the term adaptation has been used to describe neural processes (peripheral and cerebral) that constitute this decrease in behavioral response. Working with humans, the observation of reduced intensity (perception of the strength of an odor) is a typical habituation measure (follows the 10 rules of Rankin et al. [69]), while direct reductions of peripheral and central processes constitute adaptation. Therefore, in this review, the term habituation was used to describe changes in perceptual intensity. Furthermore, decreases of neuronal responses pre- and post-glomerular neurons are termed peripheral adaptation and central adaptation respectively. Finally the term "odor" defines the perception of sensation evoked by chemosensory stimulation, while the term "odorant" represents the molecule evoking the odor.

All sensory functions, alone or in combination with others, produce adaptation and thus modify the perception and possible consequent behaviors to create habituation. The ability to discern changes in our environment with all senses is crucial for survival and explains why forms of habituation can be seen in single cell organisms, e.g. amoeba and paramecium [31]. For instance, rapid visual adaptation is required to efficiently encode the several inputs encountered in a single visual scene to promote visually guided behavior. Here, adaptation affects the neurons accepting the visual stimuli (i.e. the retina), adjusts brain processing to the current environment, and thus improves performance in the visual task at hand. Similarly, the olfactory system continually encounters a wide variety of odorants (possibly more than a trillion [7]; but see also [21]) and a mechanism must exist to segment them, otherwise the system would be overwhelmed with stimulation. Here, adaptation acts as a short-term filter, thus reducing perception to ambient odorants, possibly through inhibiting central processes, to reduce odor perception (i.e. habituate) and respond to more novel

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odorants. For example, without habituation to natural smells in the environment the detection of more immediate threats, such as odors relating to fires or enemies, or the presence of nearby rewards, such as food, would be severely impaired [13]. In the short term, adaptation may also contribute to background segmentation, where the nose unlike the eyes cannot determine new and already present odorants that are inhaled simultaneously, and must instead rely on rapid adaptation to separate changing odors from constant and non-informative ones [29,41,55,91].

To date, there have been several reviews of sensory adaptation with most of them exclusively covering vision [14,47,70,72,76,81,94] and hearing [22,81,94], leaving the senses of touch, taste and smell with limited reviews that look at sensory-specific adaptations [16,58,61,97]. This review intends to partially fill this gap, providing an overview of the past and current research dealing with habituation and adaptation in humans. This non-systematic review of the field discusses underlying processes of adaptation at the peripheral and central nervous system and modalities of measurement for each, and then describes olfactory habituation principles.

2. Olfactory adaptation in humans

Investigations into the phenomenon of human olfactory adaptation began with behavioral and psychophysical measurements. For example, studies evaluating absolute threshold or intensity often used reaction times or asked participants to scale or rate their experience. Although these measurements are reliable for testing broad concepts they cannot account for measurements beyond behavioral responsiveness such as the cessation of smell (ATCS) nor can they pinpoint the adaptation of neural features that are causing perceptual changes. Today still a debate exists on how each site (peripheral and cerebral) is involved during the adaptation processes to create habituation. To focus on this issue and get a cleaner picture of perception, behavioral research has shifted to cellular and molecular techniques (e.g. single-cell recordings) in animals (e.g., [102]). However, studying olfaction in humans does not typically allow such precise, intrusive recordings and other, less invasive techniques have to be used. Next, we will explore some of the more modern techniques and their contribution to understanding olfactory adaptation at the peripheral and cerebral level.

2.1. Peripheral adaptation

Odorants may come into contact with olfactory receptor neurons (ORNs) through two pathways: retronasally and orthonasally. Retronasal olfaction occurs when odorants enter the mouth and propagates to the nasal cavity through the back of the nose (the nasopharynx) while odorants that are inhaled through the nose passively by smelling or actively by sniffing represent orthonasal olfaction [78]. Additionally, active smelling (i.e. “sniffing”) through orthonasal olfaction influences adaptation in ORNs by changing the amount of odorant that reaches the olfactory epithelium [4]; however, this effect has been shown mostly in rat models and more human studies are needed [57,92].

Early threshold studies implicated the periphery as the site of adaptation. These studies measured adaptation effects across sites where one nostril was adapted and then the same (ipsilateral) and opposite (contralateral) sites were tested for threshold sensitivity and recovery (e.g., [19,46]). The olfactory epithelium is separated by the septum to form a left and right epithelium. Therefore, olfactory stimulation of one side produces little or no activation in the other side (for example, in patients with no olfactory function on one side this can be shown very nicely: [95]). Following complete habituation to an odorant exposed to one nostril, if subjects report a decrease of intensity when sniffing again the odorant with the other nostril, then adaption is cerebral but does not exclude peripheral adaptation; if subjects do not report a decrease of intensity when smelling with the non-adapted nostril, then adaptation is only peripheral and the central nervous system is not involved at all. The results of three studies using this method showed that subjects habituated after mono-rhinal exposure to an odorant; although the contralateral nostril was less adapted and recovered more quickly than the ipsilateral side, revealing the influence of cerebral adaptation but not excluding the peripheral one [9,46,86].

Measurements in humans are necessarily less invasive than measurements in animals, which limits the options to gain exact insight into neural processes. However, the electro-olfactogram (EOG) is a validated technique in humans that represents the summated generator potentials of olfactory receptor neurons in response to an olfactory stimulus [28,42,51]. EOG measurements provide an opportunity of recording neuronal input from the peripheral olfactory system during adaptation while simultaneously obtaining psychophysical responses in awake humans. For example, EOG experiments have shown that rapid adaptation (2 repetitions) does not occur in the periphery and EOG can still be obtained from stimuli that the subjects could not even perceive [34,36]. Studies also show that perceived intensities decrease more quickly than electrical peripheral recordings (see also [56]). Lastly, EOG recorded in response to orthonasal stimulation show larger amplitudes than recordings in response to retronasal stimulation, yet no studies have looked at adaptation effects from retronasally presented odors using EOG [37].

2.2. Central adaptation

Human studies have shown that the central nervous system plays a pivotal role in olfactory adaptation, quickly filtering out external stimuli to notice and process new ones [34,36]. Nervous system components involved in adaptation include the piriform cortex, orbitofrontal cortex, amygdala, temporal lobe and anterior hippocampus as shown in humans [54,66] and animals [41,98]. Although in animal studies, the olfactory bulb (OB) shows little adaptation [101], the piriform cortex showed adaptation, in rats, after 30s of continuous exposure [98]. In humans the piriform cortex showed habituation within 60s of stimulation while orbitofrontal cortex was significantly activated during the whole exposure. Thus, orbitofrontal cortex may control olfactory inputs from piriform cortex, likely through inhibitory connections. Additionally, subcortical components have been shown responsible for particular processes of olfactory adaptation while the role of others is more elusive. For example, core components of the primary olfactory cortex (POC) like the piriform cortex have been associated with odor-background segmentation in animal and human models while habituating roles of the hippocampus and anterior insula are not known [41,80]. However, similar to peripheral adaptation, research for central adaptation processing has focused mostly on animal models with only a handful of human studies.

A popular non-invasive tool for in vivo imaging of biological activity among human brains has been functional magnetic resonance imaging (fMRI) [26,90]. For this approach, the blood-oxygenation level detection (BOLD) response is used as an indirect measurement of neural activation. Early fMRI recordings yielded small or no activation in areas of the POC in response to odorants. Sobel et al. [80] stated this was due to two issues: 1) odorant-induced neural activity in POC does not induce an overall local increase in blood flow and 2) odorant-induced neural activity in POC does induce an increase in blood flow, but the time course of the increase differs from the time course of odorant stimulation. To test the later, Sobel and colleagues consequently created a design to measure adaptation. Their results showed a consistent early increased activation in the POC followed by adaptation, or decrease of signal, of the same area after 30–40 s. Here, they demonstrated that rapid adaptation takes place in the POC, especially the piriform cortex, and must be accounted for in designs and analysis [80]. These results were later validated by other studies showing similar areas that initially increased and then decreased in BOLD response during prolonged odorous stimulation, and pointed out a