Accepted Manuscript

Habituation and adaptation to odors in humans

R. Pellegrino, C. Sinding, R.A. de Wijk, T. Hummel

PII: S0031-9384(16)30727-2
DOI: doi: 10.1016/j.physbeh.2017.04.006
Reference: PHB 11765

To appear in: *Physiology & Behavior*

Received date: 25 August 2016
Revised date: 28 March 2017
Accepted date: 8 April 2017

Please cite this article as: R. Pellegrino, C. Sinding, R.A. de Wijk, T. Hummel , Habituation and adaptation to odors in humans. The address for the corresponding author was captured as affiliation for all authors. Please check if appropriate. Phb(2017), doi: 10.1016/j.physbeh.2017.04.006

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Habituation and adaptation to odors in humans

Pellegrino R[1], Sinding C[1,2], de Wijk RA[3] and Hummel T[1]

[1] Interdisciplinary Center on Smell & Taste, Department of Otorhinolaryngology, TU Dresden, Dresden, Germany

[2] Centre des Sciences du Goût et de l'Alimentation, CNRS, UMR 6265, INRA, UMR 1324, Université de Bourgogne, Dijon, France

[3] Wageningen Food & Biobased Research, Wageningen, The Netherlands

Keywords: smell, olfaction, human, desensitization, adaptation, neuroscience

Running title: Habituation and adaptation to odors

Correspondence to: Thomas Hummel, M.D., Smell & Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Fetscherstrasse 74, 01307 Dresden, Germany; thummel@mail.zih.tu-dresden.de

Acknowledgement: Preparation of this manuscript was supported by Unilever, Port Sunlight, UK.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

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.

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Introduction

Thompson and Spencer determined in the late 60s the nine behavioral principles of habituation in a landmark paper (Thompson & Spencer, 1966), and these principles were repeated and expanded upon by Groves and Thompson in 1970 (Groves & Thompson, 1970). 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 (Rankin et al., 2010). 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. (2010)], 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

ACCEPTED MANUSCRIPT

paramecium (Harris, 1943). 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 (Bushdid et al., 2014); but see also (Dunkel et al., 2014)] 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 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 (Christensen, Heinbockel, & Hildebrand, 1996). 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 (Gottfried, 2010; Kadohisa & Wilson, 2006; Linster, Henry, Kadohisa, & Wilson, 2007; Uchida, Kepecs, & Mainen, 2006).

To date, there have been several reviews of sensory adaptation with most of them exclusively covering vision (Clifford et al., 2007; Kohn, 2007; Rieke & Rudd, 2009; S, L, & A, 2008; Shapley & Enroth-Cugell, 1984; Solomon & Kohn, 2014; Wark, Lundstrom, & Fairhall, 2007) and hearing (Eggermont, 1985; Solomon & Kohn, 2014; Wark et al., 2007), leaving the senses of touch, taste and smell with limited reviews that look at sensory-specific adaptations (Dalton, 2000; McLaughlin, 1993; O'Mahony, 1979; Wilson, 2009). This review intends to partially fill this gap, providing an overview of the past and current research

ACCEPTED MANUSCRIPT

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.

Olfactory adaptation

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., Zufall & Leinders-Zufall, 2000). 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.

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)

ACCEPTED MANUSCRIPT

while odorants that are inhaled through the nose passively by smelling or actively by sniffing represent orthonasal olfaction (Small, Gerber, Mak, & Hummel, 2005). Additionally, active smelling (i.e. "sniffing") through orthonasal olfaction influences adaptation in ORNs by changing the amount of odorant that reaches the olfactory epithelium (Beauchamp, Scheibe, Hummel, & Buettner, 2014); however, this effect has been shown mostly in rat models and more human studies are needed (Mainland & Sobel, 2006; Verhagen, Wesson, Netoff, White, & Wachowiak, 2007).

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., Köster, 1971; de Wijk, 1989). 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: (Welge-Luessen et al., 2001)]. 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 (Cain, 1977; Köster, 1971; Stuiver, 1958).

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-

ACCEPTED MANUSCRIPT

olfactogram (EOG) is a validated technique in humans that represents the summated generator potentials of olfactory receptor neurons in response to an olfactory stimulus (Getchell & Shepherd, 1978; Kobal, 1981; Lapid & Hummel, 2013). 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 (Hummel et al. 1996; Hummel et al. 2006). Studies also show that perceived intensities decrease more quickly than electrical peripheral recordings [see also (Lorig, 2000)] 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 (Hummel, Seo, Pellegrino, & Heilmann, 2016).

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 (Hummel et al., 1996;Hummel, Mojet, & Kobal, 2006). Nervous system components involved in adaptation include the piriform cortex, orbitofrontal cortex, amygdala, temporal lobe and anterior hippocampus as shown in humans (Li, Luxenberg, Parrish, & Gottfried, 2006; Poellinger et al., 2001) and animals (Kadohisa & Wilson, 2006; Wilson, 1998). Although in animal studies, the olfactory bulb (OB) shows little adaptation, (Zhao et al., 2015), the piriform cortex showed adaptation, in rats, after 30s of continuous exposure (Wilson, 1998). In humans the piriform cortex showed habituation within 60s of stimulation while

ACCEPTED MANUSCRIPT

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 (Kadohisa & Wilson, 2006; Sobel et al., 2000). 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) (Friston et al., 1998; Toro, Fox, & Paus, 2008). 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. (2000) 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 seconds. Here, they demonstrated that rapid adaptation takes place in the POC, especially the piriform cortex, and must be accounted for in designs and analysis (Sobel et al., 2000). 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

ACCEPTED MANUSCRIPT

similar trend for the hippocampus and anterior insula while the OFC exhibited a sustained increase in activation (Li et al., 2006; Poellinger et al., 2001).

Studies have recently utilized EEG which allows examination of sequential processing of information with a high temporal resolution. EEG, along with its event-related aspects, provides a considerable direct and noninvasive technique that reflects the immediate mass action of neural networks from a wide range of brain systems (Michel, Koenig, Brandeis, Gianotti, & Wackermann, 2009). Olfactory event-related potential (OERP) measurements are recorded in response to odors embedded in a constant air-flow (Kobal & Hummel, 1988). OERP consist of early and late components. The early components (P1 and N1) have been reported to represent more the physical response to a stimulus (e.g. odorant concentration) while late components (P2 and P3) to a higher degree reflect internal response such as novelty, familiarity or pleasantness (Duncan-Johnson & Donchin, 1977; Kobal, Hummel, & Van Toller, 1992; Lorig, 2000; Rombaux, Huart, & Mouraux, 2012).

Wang showed that olfactory adaptation is more rapid at the perceptual level (~2.5 s) than the electrophysiological (4 -10 s) with increasing stimulus frequency. Additionally, this study showed that perceived intensities completely adapted to zero, independent of pulse duration, while OERP remained at about 50 percent with increasing pulse duration (Wang, 2002). However, habituation begins after an initial decrease in OERP responses at the central level (Boesveldt, Haehner, Berendse, & Hummel, 2007). These and other olfactory studies have shown that adaptation occurs with decreased ERP amplitudes while latencies show little effect of adaptation (Croy, Maboshe, & Hummel, 2013; Scheibe, Opatz, & Hummel, 2009), even for adaptation over a prolonged period (80 mins.) (Flohr et al., 2015). Scheibe et al. (2008) additionally showed that adaptation to suprathreshold chemosensory stimuli (PEA and CO_2) seems to be independent of sex in young participants. Andersson et al. (2011), while not using a setup to test adaptation, also reported this independency (Andersson, Lundberg,

ACCEPTED MANUSCRIPT

Åström, & Nordin, 2011). Lastly, Croy et al. (2013) reported P2 amplitudes decrease over time more strongly for unpleasant (H2S) compared to pleasant odors (PEA and peach). However, the P2 latency of unpleasant odors was shorter than to pleasant odors (Croy et al., 2013).

To date, all studies on olfactory adaptation have used simple EEG protocols while several recent studies have suggested that OERPs may be localized back to their originating deep brain structures (Iannilli, Wiens, Arshamian, & Seo, 2013; Michel et al., 2009). Although this technique is still maturing, it may offer solutions to unresolved questions of olfactory adaptation. First, what are the temporal changes to olfactory pathways during increased respiration and its effects on adaptation? Secondly how does this rapid cerebral adaptation affect short-term feedback loops to the olfactory bulb thus enhancing discrimination of odor mixtures encountered in natural environments?

Olfactory habituation in humans

Although the 10 fundamental principles of habituation, as revised by Rankin et al. (2010), were defined for behavioral response decrements in unspecified sense modalities, most of these principles have been demonstrated in olfactory habituation (see Table 1). Many of these studies have concentrated on animal models (cf. review Wilson, 2009), and thus on the decrease of a specific behaviors (e.g. sniffing, go-no go) indicating a decrease of perception. However, human studies mostly measure perceptual changes rather than behavioral. We will first discuss the principles of habituation that have been studied (and neglect other principles that have not been studied for the olfactory system in humans), and then discuss other qualities and study caveats that affect olfactory perception in humans.

Principle 1: Repeated applications of a stimulus result in decreased responses

ACCEPTED MANUSCRIPT

Early models of human olfactory habituation depicted linear trends where habituation was directly proportional to odorant exposure time and reported (the possible) total disappearance of odor at certain concentration levels (Köster, 1971; Stuiver, 1958; Woodrow & Karpman, 1917). Previously Elsberg (1935) had reported a similar linear habituation trend towards a perceptual disappearance of the odor, but could not substantiate the claims that it vanished (Elsberg & Levy, 1935). However, these early studies lacked the modern instruments and knowledge of human perception. Consequently, well-controlled experiments (see *study caveats*) looking at habituation showed an exponential decline of odor intensity in respect to increased exposure to odorants, and this decreasing response did not reach zero (Ekman, Berglund, Berglund, & Lindvall, 1967). This was further supported by Cain (Cain, 1974) who had subjects freely adjust odorant concentrations to keep the odor intensity constant. However, other research from the Köster's laboratory has once again reported that the total disappearance of an odor can occur, calling the phenomenon "adaptation time required for the cessation of smell" (ATCS) (de Wijk, 1989). This difference can be explained using other measurement techniques (e.g., electro-encephalography EEG) indicating that as the detection of an odor becomes almost null, some neurons are still responsive (Wang, 2002). This may be described by the sixth characteristic of habituation which states that "repeated stimulation may continue to accumulate even after the response has reached an asymptotic level."

Principle 2: Withholding the stimulus produces recovery

After odorant exposure, the effects of olfactory habituation wear off during a recovery period, restoring the ability to notice the same odorant when encountered again. However, recovery rate from habituation is duration and concentration-dependent as shown in some studies (Cain, 1974; Ekman et al., 1967; Köster, 1971; Pryor, Steinmetz, & Stone, 1970), while recovery appeared independent of odor concentration (and odor quality) used in another study (Stuck, Fadel, Hummel, & Sommer, 2014). For short-term exposure (under a minute), partial

ACCEPTED MANUSCRIPT

recovery is almost simultaneous, called spontaneous recovery, to the removal of the odorant while maximum habituation to an odorant may take several minutes or even days to weeks for long-term exposure (e.g. present in daily environment / workplace) (Dalton & Wysocki, 1996; Gagnon, Mergler, & Lapare, 1994; Philpott, Wolstenholme, Goodenough, Clark, & Murty, 2008; Smith, Gamble, & Heil, 2010; Stuck et al., 2014). Stuck et al. (2014) looked at recovery time after habituation to two odors, phenyl ethyl alcohol (PEA) and hydrogen sulfide (H_2S), at several concentrations at prolonged exposure. They reported that, for both odorants, subjects recovered at the same rate, with odors being rated as more intense over time periods of recovery independent of the odorant. Additionally, Philpott et al. (2008) showed that the average total recovery time for PEA was 170 seconds after full habituation at prolonged exposure, and this was dependent on the subjects' age and mood. Odorous molecules do not immediately disappear after exposure like other sensory stimuli, but must be cleared from the peri-receptor environment (Dalton, 2000). Here, odor clearance may vary due to physico-chemical properties of various odorants or variation in nasal clearance mechanisms such as nasal submucosal blood flow, nasal mucociliary clearance and expiratory desorption. Similarly, variations in anatomical structure of the nasal cavity in humans, leading to differences of airflow rates, may influence recovery times (Philpott et al., 2008).

Principle 4: Increased frequency of stimulation increases habituation

To induce habituation, odorants are typically presented as a continuous stream (Dalton & Wysocki, 1996; Stone, Pryor, & Steinmetz, 1972; Stuck et al., 2014) or repeated pulses at short inter-stimulus intervals (ISI) (Cain & Polak, 1992; Hummel, Knecht, & Kobal, 1996; Jacob, Fraser, Wang, Walker, & O'Connor, 2003; Wang, 2002). In general, increased pulse length and shorter inter-stimulus intervals produce faster rates of habituation; however, Smith et al. (2010) argue that habituation through discontinuous odorant presentation may be

ACCEPTED MANUSCRIPT

confounded by aspects of recovery. Therefore, his lab introduced a new psychophysical technique for estimating the onset of odor habituation in humans through intervals of the target odorant presented over a continuous flow of the same odorant at a lower intensity (Smith et al., 2010; Yoder et al., 2014).

Principle 5: Weaker stimuli lead to more rapid habituation

The degree of habituation is influenced by the concentration of the odorant. Generally, a weak concentration will be habituated to more quickly than a stronger one relative to time and may perceptually disappear completely (Cain & Polak, 1992; Jacob et al., 2003; Stone et al., 1972; Stuck et al., 2014). However, in terms of absolute decrease, the opposite may be true with larger concentrations leading to more rapid decrease in intensity, though not to complete disappearance. For instance, Stuck et al. (2014) showed that the time to complete habituation increased with increasing odorant concentrations for PEA and H_2S, and that the odor concentration has a significant influence on the time to complete habituation. These mechanisms may be the result of receptor recruitment; increasing concentration of an odorant results in the recruitment of new olfactory receptors (Laing, Legha, Jinks, & Hutchinson, 2003). However, recovery rates from complete habituation have been shown to be independent of the odorant concentration (Stuck et al., 2014).

Principle 7: Habituation to one stimulus may generalize to other similar stimuli

Habituation has been further studied in the fields of olfactory learning and structure-activity relationships, concentrating on cross-adaptation, or the adaptive relationship between two odorants. This characteristic of adaptation is important when considering that very rarely odorants are encountered individually. Generally, odorants that are structurally similar provoke more cross-adaptation than distinct odorants, even if these odorants are discriminable (Cain & Polak, 1992; Pierce, Wysocki, Aronov, Webb, & Boden, 1996; Pierce,

ACCEPTED MANUSCRIPT

Zeng, Aronov, Preti, & Wysocki, 1995). Additionally, unfamiliar odors show more cross-adaptation (Pierce, Wysocki, & Aronov, 1993; Pierce et al., 1996), as they are less discriminable. Cross-adaptation between two odorants is not reciprocal, meaning adaptation in odorant A may induce adaptation in odorant B, but an adaptation in B may not influence adaptation in odorant A (Wilson, 2010). Furthermore, the effect of cross-adaptation is always weaker than the effect of adaptation to one odorant (Köster, 1971; de Wijk, 1989). However, most natural odors are mixtures of multiple separate odors and it is thus difficult to actually assess cross-adaptation within a natural odor.

Principle 10: *Long-term habituation*

In the revised view of habitation (Rankin et al., 2010), Rankin and colleagues acknowledged the need to define two forms of habitation, short-term and long-term habituation. Long-term habituation is demonstrated when "some stimulus repetition protocols may result in properties of the response decrement that last hours, days or weeks." In a combined field and laboratory study, Dalton and Wysocki (1996) exposed 8 individuals for two weeks at a minimum of 6 hours a day with a pleasant odor (either citralva or bornyl acetate, randomized among individuals) in their home, then tested their odor threshold and supra-threshold intensity prior to exposure, weekly during exposure and weekly (for two weeks) after exposure in the laboratory. Within a week of exposure ¾ of the individuals showed habituation to the odorant while all individuals had habituated after two weeks. Recovery rates were extended past short-term exposure with only half of the individuals showing complete recovery after two weeks, whereas one other individual showing no recovery at all. These results demonstrate the large variation in the rates of recovery among individuals after long-term exposure. Furthermore, the effect of habituation was more pronounced at threshold levels than at supra-threshold levels.

ACCEPTED MANUSCRIPT

Other odorant sensory and physicochemical characteristics that effect habituation

Among the 10 principles of habituation (Rankin et al., 2010), only one principle concerned the odorant itself: a high concentration of odorant molecules delays or decreases habituation compared to a lower concentration of the same odorant. In a recent study, the question of whether habituation differs between odorants was investigated (Sinding et al., 2017). Habituation was evaluated for 32 odorants varying in sensory (intensity, hedonicity, trigeminal activity and familiarity) and physicochemical characteristics (e.g. number of carbon atoms in the chain, number of double bonds, hydrophobicity, molecular weight, vapour pressure). Trigeminal activity appeared as a factor strongly reducing habituation as well as several physicochemical characteristics (high vapour pressure, small molecular weight, low number of double bonds). The trigeminal nerve is commonly activated by odorants and its branches are composed of different somatosensory and pain fibers that can react to texture, temperature, or chemicals. Their description can be as variable as burning, fizzy, soft, warm, cold, tingling, prickling, pungent, creamy, irritating, etc. Additionally, the trigeminal system may be seen as a sentinel of the respiratory systems, increasing arousal and decreasing habituation. For instance, repeated stimulation with high concentration of CO_2, which specifically activates trigeminal system, has been shown to activate pain fibers of the trigeminal nerve and even produce an increase in perceived intensity (Hummel, Gruber, Pauli, & Kobal, 1994). However, for CO_2 at lower concentrations the effect is different. Flohr et al. (2015) found a steeper decrease of brain activity in response to a pure "trigeminal molecule" (CO_2), compared with a relatively selective "olfactory molecule" (Phenyl Ethyl Alcohol or H_2S) (Flohr et al., 2015). Therefore, it seems that the association between the olfactory and trigeminal systems is necessary in order to see a delay of habituation. It also

ACCEPTED MANUSCRIPT

appears that the activation of the trigeminal system and potentially the affinities of odorants for receptors, mucus and odorant binding protein significantly modulate habituation.

Another important feature of odorants that may impact on habituation is their hedonicity. Odorants perceived as pleasant habituate at a slower rate, with larger differences between concentrations, than unpleasant odors (Croy et al., 2013; Jacob et al., 2003; Stuck et al., 2014). Results from these studies appear counterintuitive because unpleasant odors are associated with danger and would benefit from more initial attention, but could be explained by the decrease in that attention (Andersson, Lundberg, Åström, & Nordin, 2011) and loss of emotional salience (Schettino & Vuilleumier, 2013) over repeated exposure. Indeed, unpleasant odors may produce a relatively strong first response, involving a startle response for warning purposes, which then, because it is very strong, decreases at a faster pace than pleasant stimuli (Croy et al., 2013). Sinding et al. (2017) found contrary results, that unpleasant odorants would produce weaker habituation. However the odorants that were unpleasant were also more trigeminal. Therefore, pleasantness alone may not be a relevant factor for modulating the rate of habituation, and only a combination of factors may be enough informative to modulate habituation. For this reason, odorants should be carefully chosen when considered for a habituation study, especially when comparing these results across other studies.

Study caveats

Several experimental biases are entangled with the study of habituation and modulate the responses to odorous stimuli. For example, asking subjects to report "when the odor disappears" falsely facilitates total disappearance of odor to prolonged exposure because it is expected by the subject (Cain, 1974). Additionally, priming effects such as explanations given to the subject on the biological importance of the odor (e.g. hazardous, relaxing, etc.)

ACCEPTED MANUSCRIPT

may considerably modify adaptation. For instance, a novel odor that is perceived as hazardous reduces or delays perceived adaptation to that odor in comparison to perceiving the same odor under the context that it is beneficial or neutral (Dalton, 2000; Kobayashi et al., 2007).

Lastly, perceptual responses to olfactory stimuli require a precise production and delivery of odorants to obtain consistent results. Sight and hearing adaptation experiments can rely simply on light and tones, while chemical substances cannot as easily be directed to the olfactory epithelium. Ideally, olfactometry systems should be used controlling for stimulus steepness and timing, flow, humidity, and temperature (Kobal & Hummel, 1988).

Deficiency in habituation and adaptation

In a clinical setting, habituation may aid in diagnosis of some pathologies and impaired olfactory functionality. For instance, a large percentage (9 to 33%) of the adult population, and even higher percentage of occupational laborers, may report a chemical intolerance (CI) to odors; aspects of this are referred to as multiple chemical sensitivity (MCS) (Caress & Steinemann, 2003; Johansson, Brämerson, Millqvist, Nordin, & Bende, 2005; Kreutzer, Neutra, & Lashuay, 1999). Those considered to have MCS are not characterized by acute chemical sensitivity [e.g. increased odor intensity or decreased odor absolute detection thresholds; (Andersson, Bende, Millqvist, & Nordin, 2009)], but may have decreased olfactory habituation (Andersson et al., 2015, 2009). For example, one study exposed 18 participants with MCS and 18 healthy controls to low concentrations of the odorant n-butanol (11.5 mg/m3) for 42 minutes in an odor chamber. MCS participants reported greater perceived odor intensity, more unpleasantness and increased symptoms over time compared to controls. Similarly, throughout an OERP experiment Andersson and colleagues (2009)

ACCEPTED MANUSCRIPT

showed this effect at the central processing level with N1 amplitudes of chemical sensitive individuals remaining constant (Andersson et al., 2009).

Additionally Autism Spectrum Conditions (ASC), which are characterized by social communication difficulties alongside repetitive behaviors and special interest (APA, 2003), has been associated with sensory decline through anecdotal reports, questionnaires, and psychophysical tests (Chamak, Bonniau, Jaunay, & Cohen, 2008; Leekam, Nieto, Libby, Wing, & Gould, 2007; Suzuki, Critchley, Rowe, Howlin, & Murphy, 2003). For olfactory habituation, one study using "Sniffin' Sticks" showed that adults with ACS did not differ in threshold nor habituation (Tavassoli & Baron-Cohen, 2012). However, this study focused on adults (ages 28 – 30 years) while most studies showing olfactory dissimilarities in ASC, such as decreased olfactory identification and increased olfactory impairments, were on children and adolescents (age 10 -18 years) (Bennetto, Kuschner, & Hyman, 2007; Lane, Young, Baker, & Angley, 2010; Leekam et al., 2007).

Age-related olfactory loss has also long been reported extensively with a decline in odor identification, detection, and discrimination (Hummel, Kobal, Gudziol, & Mackay-Sim, 2007), and similarly, research has shown that older people are more prone to olfactory habituation and are slower at recovery than younger people (Stevens, Cain, & Oatley, 1989; Stevens, Cain, Schiet, & Oatley, 1989). Temporal studies have shown that older participants produce smaller N1 and P2 amplitudes with longer latencies than younger participants (Hummel, Barz, Pauli, & Kobal, 1998). For olfactory adaptation, a similar trend with age can be seen with decreased amplitudes for shorter ISIs in older males (Morgan, Covington, Geisler, Polich, & Murphy, 1997).

Future areas of research

ACCEPTED MANUSCRIPT

Several questions regarding olfactory habituation remain open. For instance, according to our literature search, some principles of habituation [set by (Thompson & Spencer, 1966)] have not been explored properly for the human olfactory system such as potentiation of habituation or habituation of dishabituation. Similarly, it is evident that odor perception involves short-term application for approach and avoidance of odorous and other environmental stimuli; however, much research is still needed to determine long-term effects of habituation specifically in odor to fully understand the added, tenth principle presented by Rankin et al (2009). Most long-term studies to date have concentrated on trigeminally active volatile organic compounds which may pose health risks, leaving many open questions pertaining to other odorants (Dalton, Dilks, & Hummel, 2006; Dalton & Wysocki, 1996; Gagnon et al., 1994; Schiffman & Williams, 2005). For instance, how does concentration and frequency of presentation of mixed odorants, which represent more realistic settings, change perception over long periods of time? More specifically to odor, which mental processes constitute the bulk of these changes (e.g. sensory adaptation, shifts in attention, odor memory)? These questions have practical importance, for example, in industry fields where workers are continually exposed to different odorants, and may help explain behavioral changes over time (Post, 1980).

Olfactory adaptation is a distributed process, operating at peripheral and central levels. For instance, research shows that ORN adapt slower and recover more quickly than central nervous system structures involved in the processing of chemosensory information (Hummel et al., 1996, 2006; Sobel et al., 2000; Wang, 2002). Here, the peripheral receptors stay responsive to all odorants while the central processing units (especially piriform cortex) rapidly adapt to the stable, less intense background focusing on identification of the new odorants presented in the foreground. However, we feel that more research is needed on the interaction of peripheral and central processes involved in adaptation and mechanisms that

ACCEPTED MANUSCRIPT

modulate this interaction. For instance, human sniffing, which increases with alertness, modulates adaptation at the peripheral and central level, but the degree to which each are impacted is not well understood. Similarly, feedback loops from peripheral to cerebral structures are not clearly defined and their role in adaptation processes are relatively unknown. Furthermore, adaptation in a realistic setting is a multisensory experience, yet little research has evaluated peripheral or the cerebral cross-adaption of olfactory activations with other senses involved in perception.

The combination of non-invasive tools, such as EOG, EEG and fMRI, with creative experimental designs offer an opportunity to answer some of these questions in humans not under anesthesia. Similarly, the increasing maturity of source localization through multi-channel EEG may help define peripheral-cerebral feedback loops involved in adaptation that happen early on in processing of chemosensory stimuli (Lascano, Hummel, Lacroix, Landis, & Michel, 2010). However, advancements in techniques and tools are still needed for an accurate portrayal of adaptation in human.

Lastly, in combination with modern measurement techniques, human studies should try to minimize variance by implementing appropriate designs to study olfaction. Whenever possible, specific olfactory or trigeminal stimuli should be chosen, and, if possible, delivered with high-precision olfactometers. Similarly, study designs focusing on characteristics of habituation should control for similar caveats specific to odors (e.g. hedonics). For instance, prolonged exposure, as stated by the fourth characteristic laid out by Rankin (Rankin et al., 2010), results in a different degree of habitation than odorants presented at varying intervals.

ACCEPTED MANUSCRIPT

References

Andersson, L., Bende, M., Millqvist, E., & Nordin, S. (2009). Attention bias and sensitization in chemical sensitivity. *Journal of Psychosomatic Research*, *66*(5), 407–16. https://doi.org/10.1016/j.jpsychores.2008.11.005

Andersson, L., Claeson, A.-S., Dantoft, T. M., Skovbjerg, S., Lind, N., & Nordin, S. (2015). Chemosensory perception, symptoms and autonomic responses during chemical exposure in multiple chemical sensitivity. *International Archives of Occupational and Environmental Health*. https://doi.org/10.1007/s00420-015-1053-y

Andersson, L., Lundberg, C., Åström, J., & Nordin, S. (2011). Chemosensory attention, habituation and detection in women and men. *International Journal of …*, *79*(2), 316–322. https://doi.org/10.1016/j.ijpsycho.2010.11.008

Beauchamp, J., Scheibe, M., Hummel, T., & Buettner, A. (2014). Intranasal Odorant Concentrations in Relation to Sniff Behavior. *Chemistry & Biodiversity*, *11*(4), 619–638. https://doi.org/10.1002/cbdv.201300320

Bennetto, L., Kuschner, E. S., & Hyman, S. L. (2007). Olfaction and taste processing in autism. *Biological Psychiatry*, *62*(9), 1015–21. https://doi.org/10.1016/j.biopsych.2007.04.019

Boesveldt, S., Haehner, A., Berendse, H. W., & Hummel, T. (2007). Signal-to-noise ratio of chemosensory event-related potentials. *Clinical Neurophysiology*, *118*(3), 690–695. https://doi.org/10.1016/j.clinph.2006.11.004

Bushdid, C., Magnasco, M. O., Vosshall, L. B., Keller, A., Pointer, M. R., Attridge, G. G., … Thomas-Danguin, T. (2014). Humans can discriminate more than 1 trillion olfactory stimuli. *Science (New York, N.Y.)*, *343*(6177), 1370–2. https://doi.org/10.1126/science.1249168

Cain, W. (1974). Perception of odor intensity and the time-course of olfactory adapation. *ASHRAE Transactions*, *80*, 53–75.

Cain, W. (1977). Bilateral interaction in olfaction. *Nature*, *268*(5615), 50–52. https://doi.org/10.1038/268050a0

Cain, W., & Polak, E. (1992). Olfactory adaptation as an aspect of odor similarity. *Chemical Senses*, *17*(5), 481–491. https://doi.org/10.1093/chemse/17.5.481

Caress, S. M., & Steinemann, A. C. (2003). A review of a two-phase population study of multiple chemical sensitivities. *Environmental Health Perspectives*, *111*(12), 1490–7. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1241652&tool=pmcentrez&rendertype=abstract

Chamak, B., Bonniau, B., Jaunay, E., & Cohen, D. (2008). What can we learn about autism from autistic persons? *Psychotherapy and Psychosomatics*, *77*(5), 271–9. https://doi.org/10.1159/000140086

Christensen, T. A., Heinbockel, T., & Hildebrand, J. G. (1996). Olfactory information processing in the brain: Encoding chemical and temporal features of odors. *Journal of Neurobiology*, *30*(1), 82–91. https://doi.org/10.1002/(SICI)1097-4695(199605)30:1<82::AID-NEU8>3.0.CO;2-C

Clifford, C. W. G., Webster, M. A., Stanley, G. B., Stocker, A. A., Kohn, A., Sharpee, T. O., & Schwartz, O. (2007). Visual adaptation: neural, psychological and computational aspects. *Vision Research*, *47*(25), 3125–31. https://doi.org/10.1016/j.visres.2007.08.023

Croy, I., Maboshe, W., & Hummel, T. (2013). Habituation effects of pleasant and unpleasant odors. *International Journal of Psychophysiology : Official Journal of the International Organization of Psychophysiology*, *88*(1), 104–8. https://doi.org/10.1016/j.ijpsycho.2013.02.005

ACCEPTED MANUSCRIPT

Dalton, P. (2000). Psychophysical and behavioral characteristics of olfactory adaptation. *Chemical Senses*, *25*(4), 487–92. https://doi.org/10.1093/chemse/25.4.487

Dalton, P., Dilks, D., & Hummel, T. (2006). Effects of long-term exposure to volatile irritants on sensory thresholds, negative mucosal potentials, and event-related potentials. *Behavioral Neuroscience*, *120*(1), 180.

Dalton, P., & Wysocki, C. J. (1996). The nature and duration of adaptation following long-term odor exposure. *Perception & Psychophysics*, *58*(5), 781–792. https://doi.org/10.3758/BF03213109

de Wijk, R. A. (1989). Temporal factors in human olfactory perception. *Unpublished Doctoral Dissertation*. *University of Utrech*.

Duncan-Johnson, C. C., & Donchin, E. (1977). On Quantifying Surprise: The Variation of Event-Related Potentials With Subjective Probability. *Psychophysiology*, *14*(5), 456–467. https://doi.org/10.1111/j.1469-8986.1977.tb01312.x

Dunkel, A., Steinhaus, M., Kotthoff, M., Nowak, B., Krautwurst, D., Schieberle, P., & Hofmann, T. (2014). Nature's Chemical Signatures in Human Olfaction: A Foodborne Perspective for Future Biotechnology. *Angewandte Chemie International Edition*, *53*(28), 7124–7143. https://doi.org/10.1002/anie.201309508

Eggermont, J. J. (1985). Peripheral auditory adaptation and fatigue: A model oriented review. *Hearing Research*, *18*(1), 57–71. https://doi.org/10.1016/0378-5955(85)90110-8

Ekman, G., Berglund, B., Berglund, U., & Lindvall, T. (1967). PERCEIVED INTENSITY OF ODOR AS A FUNCTION OF TIME OF ADAPTATION. *Scandinavian Journal of Psychology*, *8*(1), 177–186. https://doi.org/10.1111/j.1467-9450.1967.tb01392.x

Elsberg, C. A., & Levy, I. (1935). The sense of smell: I. A new and simple method of quantitative olfactometry. *Bull Neurol Inst NY*, *4*, 5–19.

Flohr, E. L. R., Boesveldt, S., Haehner, A., Iannilli, E., Sinding, C., & Hummel, T. (2015). Time-course of trigeminal versus olfactory stimulation: Evidence from chemosensory evoked potentials. *International Journal of Psychophysiology*, (October), 1–7. https://doi.org/10.1016/j.ijpsycho.2015.01.014

Friston, K. J., Fletcher, P., Josephs, O., Holmes, A., Rugg, M. D., & Turner, R. (1998). Event-related fMRI: characterizing differential responses. *NeuroImage*, *7*(1), 30–40. https://doi.org/10.1006/nimg.1997.0306

Gagnon, P., Mergler, D., & Lapare, S. (1994). Olfactory adaptation, threshold shift and recovery at low levels of exposure to methyl isobutyl ketone (MIBK). *Neurotoxicology*, *15*(3), 637–42. Retrieved from http://europepmc.org/abstract/med/7854600

Getchell, T. V, & Shepherd, G. M. (1978). Adaptive properties of olfactory receptors analysed with odour pulses of varying durations. *The Journal of Physiology*, *282*, 541–60. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/722560

Gottfried, J. A. (2010). Central mechanisms of odour object perception. *Nature Reviews. Neuroscience*, *11*(9), 628–41. https://doi.org/10.1038/nrn2883

Groves, P. M., & Thompson, R. F. (1970). Habituation: a dual-process theory. *Psychological Review*, *77*(5), 419–50. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/4319167

Harris, J. D. (1943). Habituatory response decrement in the intact organism. *Psychological Bulletin*, *40*(6), 385–422.

Hummel, T., Barz, S., Pauli, E., & Kobal, G. (1998). Chemosensory event-related potentials change with age. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *108*(2), 208–217. https://doi.org/10.1016/S0168-5597(97)00074-9

ACCEPTED MANUSCRIPT

Hummel, T., Gruber, M., Pauli, E., & Kobal, G. (1994). Chemo-somatosensory event-related potentials in response to repetitive painful chemical stimulation of the nasal mucosa. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *92*(5), 426–432. https://doi.org/10.1016/0168-5597(94)90020-5

Hummel, T., Knecht, M., & Kobal, G. (1996). Peripherally obtained electrophysiological responses to olfactory stimulation in man: electro-olfactograms exhibit a smaller degree of desensitization compared with subjective intensity estimates. *Brain Research*, *717*(1–2), 160–164. https://doi.org/10.1016/0006-8993(96)00094-7

Hummel, T., Kobal, G., Gudziol, H., & Mackay-Sim, A. (2007). Normative data for the "Sniffin' Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. *European Archives of Oto-Rhino-Laryngology : Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : Affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery*, *264*(3), 237–43. https://doi.org/10.1007/s00405-006-0173-0

Hummel, T., Mojet, J., & Kobal, G. (2006). Electro-olfactograms are present when odorous stimuli have not been perceived. *Neuroscience Letters*, *397*(3), 224–8. https://doi.org/10.1016/j.neulet.2005.12.048

Hummel, T., Seo, H.-S., Pellegrino, R., & Heilmann, S. (2016). Electro-Olfactograms in Humans in Response to Ortho- and Retronasal Chemosensory Stimulation. *Chemosensory Perception*, 1–5. https://doi.org/10.1007/s12078-016-9217-z

Iannilli, E., Wiens, S., Arshamian, A., & Seo, H.-S. (2013). A spatiotemporal comparison between olfactory and trigeminal event-related potentials. *NeuroImage*, *77*, 254–61. https://doi.org/10.1016/j.neuroimage.2012.12.057

Jacob, T. J. ., Fraser, C., Wang, L., Walker, V., & O'Connor, S. (2003). Psychophysical evaluation of responses to pleasant and mal-odour stimulation in human subjects; adaptation, dose response and gender differences. *International Journal of Psychophysiology*, *48*(1), 67–80. https://doi.org/10.1016/S0167-8760(03)00020-5

Johansson, A., Brämerson, A., Millqvist, E., Nordin, S., & Bende, M. (2005). Prevalence and risk factors for self-reported odour intolerance: the Skövde population-based study. *International Archives of Occupational and Environmental Health*, *78*(7), 559–64. https://doi.org/10.1007/s00420-005-0616-8

Kadohisa, M., & Wilson, D. A. (2006). Olfactory cortical adaptation facilitates detection of odors against background. *Journal of Neurophysiology*, *95*(3), 1888–96. https://doi.org/10.1152/jn.00812.2005

Kobal, G. (1981). Elektrophysiologische untersuchungen des menschlichen geruchssinns. *Thieme*.

Kobal, G., & Hummel, C. (1988). Cerebral chemosensory evoked potentials elicited by chemical stimulation of the human olfactory and respiratory nasal mucosa. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *71*(4), 241–250. https://doi.org/10.1016/0168-5597(88)90023-8

Kobal, G., Hummel, T., & Van Toller, S. (1992). Differences in human chemosensory evoked potentials to olfactory and somatosensory chemical stimuli presented to left and right nostrils. *Chemical Senses*, *17*(3), 233–244. https://doi.org/10.1093/chemse/17.3.233

Kobayashi, T., Sakai, N., Kobayakawa, T., Akiyama, S., Toda, H., & Saito, S. (2007). Effects of Cognitive Factors on Perceived Odor Intensity in Adaptation/Habituation Processes: from 2 Different Odor Presentation Methods. *Chemical Senses*, *33*(2), 163–171. https://doi.org/10.1093/chemse/bjm075

ACCEPTED MANUSCRIPT

Koester, E. P. (1971). *Adaptation and Cross-adaptation of Olfaction*. Bronder.

Kohn, A. (2007). Visual adaptation: physiology, mechanisms, and functional benefits. *Journal of Neurophysiology*, *97*(5), 3155–64. https://doi.org/10.1152/jn.00086.2007

Kreutzer, R., Neutra, R. R., & Lashuay, N. (1999). Prevalence of People Reporting Sensitivities to Chemicals in a Population based Survey. *American Journal of Epidemiology*, *150*(1), 1–12. https://doi.org/10.1093/oxfordjournals.aje.a009908

Laing, D. G., Legha, P. K., Jinks, A. L., & Hutchinson, I. (2003). Relationship between molecular structure, concentration and odor qualities of oxygenated aliphatic molecules. *Chemical Senses*, *28*(1), 57–69. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12502524

Lane, A. E., Young, R. L., Baker, A. E. Z., & Angley, M. T. (2010). Sensory processing subtypes in autism: association with adaptive behavior. *Journal of Autism and Developmental Disorders*, *40*(1), 112–22. https://doi.org/10.1007/s10803-009-0840-2

Lapid, H., & Hummel, T. (2013). Recording odor-evoked response potentials at the human olfactory epithelium. *Chemical Senses*, *38*(1), 3–17. https://doi.org/10.1093/chemse/bjs073

Lascano, A. M., Hummel, T., Lacroix, J.-S., Landis, B. N., & Michel, C. M. (2010). Spatio-temporal dynamics of olfactory processing in the human brain: an event-related source imaging study. *Neuroscience*, *167*(3), 700–8. https://doi.org/10.1016/j.neuroscience.2010.02.013

Leekam, S. R., Nieto, C., Libby, S. J., Wing, L., & Gould, J. (2007). Describing the sensory abnormalities of children and adults with autism. *Journal of Autism and Developmental Disorders*, *37*(5), 894–910. https://doi.org/10.1007/s10803-006-0218-7

Li, W., Luxenberg, E., Parrish, T., & Gottfried, J. A. (2006). Learning to smell the roses: experience-dependent neural plasticity in human piriform and orbitofrontal cortices. *Neuron*, *52*(6), 1097–108. https://doi.org/10.1016/j.neuron.2006.10.026

Linster, C., Henry, L., Kadohisa, M., & Wilson, D. A. (2007). Synaptic adaptation and odor-background segmentation. *Neurobiology of Learning and Memory*, *87*(3), 352–60. https://doi.org/10.1016/j.nlm.2006.09.011

Lorig, T. S. (2000). The application of electroencephalographic techniques to the study of human olfaction: A review and tutorial. *International Journal of Psychophysiology*, *36*(2), 91–104. https://doi.org/10.1016/S0167-8760(99)00104-X

Mainland, J., & Sobel, N. (2006). The sniff is part of the olfactory percept. *Chemical Senses*, *31*(2), 181–96. https://doi.org/10.1093/chemse/bjj012

McLaughlin, D. (1993). Evoked potentials as indices of adaptation in the somatosensory system in humans: A review and prospectus☆. *Brain Research Reviews*, *18*(2), 151–206. https://doi.org/10.1016/0165-0173(93)90001-G

Michel, C. M., Koenig, T., Brandeis, D. B., Gianotti, L. R. R., & Wackermann, J. (2009). *Electrical neuroimaging*. *Book*. https://doi.org/10.1017/CBO9780511596889

Morgan, C. D., Covington, J. W., Geisler, M. W., Polich, J., & Murphy, C. (1997). Olfactory event-related potentials: older males demonstrate the greatest deficits. *Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section*, *104*(4), 351–358. https://doi.org/10.1016/S0168-5597(97)00020-8

O'Mahony, M. (1979). Salt taste adaptation: the psychophysical effects of adapting solutions and residual stimuli from prior tastings on the taste of sodium chloride. *Perception*, *8*(4), 441–476. https://doi.org/10.1068/p080441

Philpott, C. M., Wolstenholme, C. R., Goodenough, P. C., Clark, A., & Murty, G. E. (2008).

ACCEPTED MANUSCRIPT

Olfactory clearance: what time is needed in clinical practice? *The Journal of Laryngology and Otology*, *122*(9), 912–7. https://doi.org/10.1017/S0022215107000977

Pierce, J. D., Wysocki, C. J., & Aronov, E. V. (1993). Mutual cross-adaptation of the volatile steroid androstenone and a non-steroid perceptual analog. *Chemical Senses*, *18*(3), 245–256. https://doi.org/10.1093/chemse/18.3.245

Pierce, J. D., Wysocki, C. J., Aronov, E. V., Webb, J. B., & Boden, R. M. (1996). The role of perceptual and structural similarity in cross-adaptation. *Chemical Senses*, *21*(2), 223–237. https://doi.org/10.1093/chemse/21.2.223

Pierce, J. D., Zeng, X.-N., Aronov, E. V, Preti, G., & Wysocki, C. J. (1995). Cross-adaptation of Sweaty-smelling 3-methyl-2- hexenoic Acid by a Structurally-similar, Pleasant-smelling Odorant. *Chemical Senses*, *20*(4), 401–411. https://doi.org/10.1093/chemse/20.4.401

Poellinger, a, Thomas, R., Lio, P., Lee, a, Makris, N., Rosen, B. R., & Kwong, K. K. (2001). Activation and habituation in olfaction--an fMRI study. *NeuroImage*, *13*(4), 547–560. https://doi.org/10.1006/nimg.2000.0713

Post, R. M. (1980). Intermittent versus continuous stimulation: Effect of time interval on the development of sensitization or tolerance. *Life Sciences*, *26*(16), 1275–1282. https://doi.org/10.1016/0024-3205(80)90085-5

Pryor, G. T., Steinmetz, G., & Stone, H. (1970). Changes in absolute detection threshold and in subjective intensity of suprathreshold stimuli during olfactory adaptation and recovery. *Perception & Psychophysics*, *8*(5), 331–335. https://doi.org/10.3758/BF03212603

Rankin, C. H., Abrams, T., Barry, R. J., Bhatnagar, S., Clayton, D., Colombo, J., … Thompson, R. F. (2010). Habituation Revisited: An Updated and Revised Description of the Behavioral Characteristics of Habituation, *92*(2), 135–138. https://doi.org/10.1016/j.nlm.2008.09.012.Habituation

Rieke, F., & Rudd, M. E. (2009). The challenges natural images pose for visual adaptation. *Neuron*, *64*(5), 605–16. https://doi.org/10.1016/j.neuron.2009.11.028

Rombaux, P., Huart, C., & Mouraux, a. (2012). Assessment of chemosensory function using electroencephalographic techniques. *Rhinology*, *50*(12), 13–21. https://doi.org/10.4193/Rhino11.126

S, W., L, M., & A, K. (2008). Functional magnetic resonance adaptation in visual neuroscience. *Reviews in the Neurosciences*, *19*(19), 363–380. Retrieved from http://pubmed.cn/19145990

Scheibe, M., Opatz, O., & Hummel, T. (2009). Are there sex-related differences in responses to repetitive olfactory/trigeminal stimuli? *European Archives of Oto-Rhino-Laryngology : Official Journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : Affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery*, *266*(8), 1323–6. https://doi.org/10.1007/s00405-008-0860-0

Schettino, A., & Vuilleumier, P. (2013). Brain mechanisms for emotional influences on perception and attention: What is magic and what is not. *Biological Psychology*, *92*(3), 492–512. https://doi.org/10.1016/j.biopsycho.2012.02.007

Schiffman, S. S., & Williams, C. M. (2005). Science of odor as a potential health issue. *Journal of Environmental Quality*, *34*(1), 129–138.

Shapley, R., & Enroth-Cugell, C. (1984). Visual adaptation and retinal gain controls. *Progress in Retinal Research*, *3*, 263–346. Retrieved from http://cat.inist.fr/?aModele=afficheN&cpsidt=9015259

Sinding, C., Valadier, F., Al-Hassani, V., Feron, G., Tromelin, A., Kontaris, I., … Wehrens, R.

ACCEPTED MANUSCRIPT

(2017). New determinants of olfactory habituation. *Scientific Reports*, *7*, 41047. https://doi.org/10.1038/srep41047

Small, D. M., Gerber, J. C., Mak, Y. E., & Hummel, T. (2005). Differential neural responses evoked by orthonasal versus retronasal odorant perception in humans. *Neuron*, *47*(4), 593–605. https://doi.org/10.1016/j.neuron.2005.07.022

Smith, D. W., Gamble, K. R., & Heil, T. A. (2010). A Novel Psychophysical Method for Estimating the Time Course of Olfactory Rapid Adaptation in Humans. *Chemical Senses*, *35*(8), 717–725. https://doi.org/10.1093/chemse/bjq073

Sobel, N., Prabhakaran, V., Zhao, Z., Desmond, J. E., Glover, G. H., Sullivan, E. V, & Gabrieli, J. D. (2000). Time course of odorant-induced activation in the human primary olfactory cortex. *J Neurophysiol*, *83*(1), 537–551. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10634894

Solomon, S. G., & Kohn, A. (2014). Moving sensory adaptation beyond suppressive effects in single neurons. *Current Biology : CB*, *24*(20), R1012-22. https://doi.org/10.1016/j.cub.2014.09.001

Stevens, J. C., Cain, W. S., & Oatley, M. W. (1989). Aging Speeds Olfactory Adaptation and Slows Recovery. *Annals of the New York Academy of Sciences*, *561*(1 Nutrition and), 323–325. https://doi.org/10.1111/j.1749-6632.1989.tb20994.x

Stevens, J., Cain, W., Schiet, F., & Oatley, M. (1989). Olfactory adaptation and recovery in old age. *Perception*, *18*(2), 265–276. https://doi.org/10.1068/p180265

Stone, H., Pryor, G. T., & Steinmetz, G. (1972). A comparison of olfactory adaptation among seven odorants and their relationship with several physicochemical properties. *Perception & Psychophysics*, *12*(6), 501–504. https://doi.org/10.3758/BF03210944

Stuck, B. A., Fadel, V., Hummel, T., & Sommer, J. U. (2014). Subjective Olfactory Desensitization and Recovery in Humans, 151–157. https://doi.org/10.1093/chemse/bjt064

Stuiver, M. (1958). *Biophysics of the sense of smell*. *Excelsior*. University of Groningen.

Suzuki, Y., Critchley, H. D., Rowe, A., Howlin, P., & Murphy, D. G. M. (2003). Impaired Olfactory Identification in Asperger's Syndrome. *The Journal of Neuropsychiatry and Clinical Neurosciences*. Retrieved from http://neuro.psychiatryonline.org/doi/10.1176/jnp.15.1.105

Tavassoli, T., & Baron-Cohen, S. (2012). Olfactory detection thresholds and adaptation in adults with autism spectrum condition. *Journal of Autism and Developmental Disorders*, *42*(6), 905–909. https://doi.org/10.1007/s10803-011-1321-y

Thompson, R. F., & Spencer, W. A. (1966). Habituation: a model phenomenon for the study of neuronal substrates of behavior. *Psychological Review*, *73*(1), 16–43. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/5324565

Toro, R., Fox, P. T., & Paus, T. (2008). Functional coactivation map of the human brain. *Cerebral Cortex (New York, N.Y. : 1991)*, *18*(11), 2553–9. https://doi.org/10.1093/cercor/bhn014

Uchida, N., Kepecs, A., & Mainen, Z. F. (2006). Seeing at a glance, smelling in a whiff: rapid forms of perceptual decision making. *Nature Reviews. Neuroscience*, *7*(6), 485–91. https://doi.org/10.1038/nrn1933

Verhagen, J. V, Wesson, D. W., Netoff, T. I., White, J. A., & Wachowiak, M. (2007). Sniffing controls an adaptive filter of sensory input to the olfactory bulb. *Nature Neuroscience*, *10*(5), 631–9. https://doi.org/10.1038/nn1892

Wang, L. (2002). The correlation between physiological and psychological responses to odour stimulation in human subjects. *Clinical Neurophysiology*, *113*(4), 542–551.

ACCEPTED MANUSCRIPT

https://doi.org/10.1016/S1388-2457(02)00029-9

Wark, B., Lundstrom, B. N., & Fairhall, A. (2007). Sensory adaptation. *Current Opinion in Neurobiology*, *17*(4), 423–9. https://doi.org/10.1016/j.conb.2007.07.001

Welge-Luessen, A., Temmel, A., Quint, C., Moll, B., Wolf, S., & Hummel, T. (2001). Olfactory function in patients with olfactory groove meningioma. *Journal of Neurology, Neurosurgery, and Psychiatry*, *70*(2), 218–21. https://doi.org/10.1136/JNNP.70.2.218

Wilson, D. (2010). Olfactory adaptation. In *Encyclopedia of perception* (pp. 676–679). Los Angelos: SAGE Publications.

Wilson, D. a. (2009). Olfaction as a model system for the neurobiology of mammalian short-term habituation. *Neurobiology of Learning and Memory*, *92*(2), 199–205. https://doi.org/10.1016/j.nlm.2008.07.010

Wilson, D. A. (1998). Habituation of Odor Responses in the Rat Anterior Piriform Cortex. *Journal of Neurophysiology*, *79*(3).

Woodrow, H., & Karpman, B. (1917). A new olfactometric technique and some results. *Journal of Experimental Psychology*, *2*(6), 431–447. https://doi.org/10.1037/h0070193

Yoder, W. M., LaRue, A. K., Rosen, J. M., Aggarwal, S., Shukla, R. M., Monir, J., & Smith, D. W. (2014). Evidence of rapid recovery from perceptual odor adaptation using a new stimulus paradigm. *Attention, Perception & Psychophysics*, *76*(4), 1093–105. https://doi.org/10.3758/s13414-013-0620-0

Zhao, F., Holahan, M. A., Houghton, A. K., Hargreaves, R., Evelhoch, J. L., Winkelmann, C. T., & Williams, D. S. (2015). Functional imaging of olfaction by CBV fMRI in monkeys: insight into the role of olfactory bulb in habituation. *NeuroImage*, *106*, 364–72. https://doi.org/10.1016/j.neuroimage.2014.12.001

Zufall, F., & Leinders-Zufall, T. (2000). The cellular and molecular basis of odor adaptation. *Chemical Senses*, *25*(4), 473–481. https://doi.org/10.1093/chemse/25.4.473

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Table 1: Rankin et al (2010) principles of habituation and adaptation as related to human olfactory research.

Characteristic	Description	Olfactory Evidence
1	Repeated application of a stimulus results in a progressive decrease in some parameter of a response to an asymptotic level. This change may include decreases in frequency and/or magnitude of the response. In many cases, the decrement is exponential, but it may also be linear; in addition, a response may show facilitation prior to decrementing because of (or presumably derived from) a simultaneous process of sensitization.	Aronsohn, 1886; Eisberg, 1935; Mulline, 1955; Ekman et al. 1967; Cain, 1974; Wijk, 1989
2	If the stimulus is withheld after response decrement, the response recovers at least partially over the observation time ("spontaneous recovery").	Pryor et al. 1970; Gagnon et al. 1994; Philpott et al. 2008; Stuck et al. 2014
3	After multiple series of stimulus repetitions and spontaneous recoveries, the response decrement becomes successively more rapid and/or more pronounced (this phenomenon can be called potentiation of habituation).	No studies
4	Other things being equal, more frequent stimulation results in more rapid and/or more pronounced response decrement, and more rapid spontaneous recovery (if the decrement has reached asymptotic levels).	Cain and Polak, 1992; Wang et al. 2002; Hummel et al. 1996; Jacob et al. 2003
5	Within a stimulus modality, the less intense the stimulus, the more rapid and/or more pronounced the behavioral response decrement. Very intense stimuli may yield no significant observable response decrement.	Stone et al. 1972; Stuck et al. 2014
6	The effects of repeated stimulation may continue to accumulate even after the response has reached an asymptotic level (which may or may not be zero, or no response). This effect of stimulation beyond asymptotic levels can alter subsequent behavior, for example, by delaying the onset of spontaneous recovery.	Wijk, 1989; Wang et al. 2002
7	Within the same stimulus modality, the response decrement shows some stimulus specificity. To test for stimulus specificity/stimulus generalization, a second, novel stimulus is presented and a comparison is made between the changes in the responses to the habituated stimulus and the novel stimulus. In many paradigms (e.g. developmental studies of language acquisition) this test has been improperly termed a dishabituation test rather than a stimulus generalization test, its proper name.	Cain and Polak, 1992; Pierce et al. 1993; Pierce et al. 1995; Pierce et al. 1996
8	Presentation of a different stimulus results in an increase of the decremented response to the original stimulus. This phenomenon is termed "dishabituation." It is important to note that the proper test for dishabituation is an increase in response to the original stimulus and not an increase in response to the dishabituating stimulus (see point #7 above). Indeed, the dishabituating stimulus by itself need not even trigger the response on its own.	No Studies

ACCEPTED MANUSCRIPT

9	Upon repeated application of the dishabituating stimulus, the amount of dishabituation produced decreases (this phenomenon can be called habituation of dishabituation).	No studies
10	Some stimulus repetition protocols may result in properties of the response decrement (e.g. more rapid rehabituation than baseline, smaller initial responses than baseline, smaller mean responses than baseline, less frequent responses than baseline) that last hours, days or weeks. This persistence of aspects of habituation is termed long-term habituation.	Gagnon et al. 1994; Dalton and Wysocki, 1996; Schiffman and Williams, 2005; Dalton and Hummel, 2011

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Highlights

- With regard to the field of olfaction several of the principles of habituation (Thompson and Spencer, 1966; Ranken et al. 2010) have either not been tested or need more research: potentiation of habituation, dishabituation, habituation of dishabituation, and long-term habituation.
- The impact of odor valence on adaptation is still not clearly understood and more research is needed in this area.
- Adaptation of odor perception is relatively fast with the onset of cortical adaptation being more pronounced than peripheral adaptation.
- Olfactory adaptation is a distributed process involving adaptation at both peripheral and cortical level, and more studies looking at feedback between these two systems (including the olfactory bulb) are needed.

ACCEPTED MANUSCRIPT